as well as autopsy findings, must, of course, be made carefully in such cases.

The reason why we decided to present only femoral vein blood is the abundance of reports indicating that peripheral blood specimens are superior to central blood as to the stability and similarity to antemortem levels of alcohols and drugs (7,9,12,15,16,18, 19,28). We think it is high time to come to a general agreement upon a standard specimen to be used for comparisons, and we believe that femoral vein blood is the best candidate.

The ratio parent drug:metabolite (P:M) should probably be used for interpretation of the kind of ingestion (29–31). High ratios may indicate an acute overdose, low ratios a high chronic dosage. However, we must keep in mind that high concentrations of both parent drug and metabolite in combination with a low P:M ratio does not exclude an acute overdose, because of the possibility of a high chronic dosage preceding an acute overdose. Conversely, a high P:M ratio may, apart from an acute overdose, also be explained by reduced metabolic capacity. The presently most studied detoxifying enzyme is Cytochrome P450 2D6, which metabolizes a number of drugs of forensic importance (32,33). Slow metabolizers will exhibit much higher ratios than rapid metabolizers, and in addition, interaction between substances with different affinity to the enzyme may also affect the ratio. As yet, no data are available concerning the possible difference in fatal levels for slow and rapid metabolizers, and we have not considered this possibility in the present work. However, the possible influence of reduced metabolization rates on the P:M ratio may affect the interpretation of the manner of death.

The benzodiazepines clonazepam, nitrazepam, and flunitrazepam are subject to a significant postmortem conversion into their 7-amino metabolites (10). We feel confident that the sum of the parent drug and metabolite is the most relevant value to be used for the toxicological interpretation.

The hypnotic drug propiomazine is also significantly degraded to the main metabolite dihydropropiomazine postmortem (unpublished observations), and the sum of parent drug and metabolite would probably be the measure of choice also in this case.

Special caution should be used when considering the values of substances with a low number of included cases, because small samples will always carry a risk of yielding averages differing from what it would be if more cases were included. It is also difficult to identify outlayers if comparable reference data are lacking. For example, only one A case involving chlordiazepoxide could be included, and this value is probably not representative for most fatal cases.

There is always a risk that the lowest reported fatal value of a certain substance will be quoted. However, low extremes may be explained by anaphylaxis, idiosyncracy, or similar rare conditions, and would not be expected in the average routine case. Therefore, in Table 1, we have presented percentiles or quartiles instead of lowest and highest values (with some exceptions due to insufficient data), because such a presentation gives a more accurate view of the distribution of the values. Thus, data in the columns LOW and HIGH in the table do not represent the lowest or highest values found if the number of cases in the particular group is equal to or exceeds four.

Table 3 displays the panorama of postmortem toxicology in Sweden, which fairly well reflects the changes in therapy traditions over time, at least as far as neuroleptics, benzodiazepines, antidepressants, and analgesics are concerned.

It is tempting to compare the number of fatal cases for a certain substance in Table 1 with the number of positive detections in Table 3. However, the objective of this study was not to identify substances considered to be particularly dangerous or especially harmless, and the methods of selection make the accuracy of such a comparison doubtful. The numbers of excluded intoxications differ considerably among drugs, and in addition, some drugs may show a high number of B cases because of their occurrence in combination preparations. Thus, we dissuade the reader from making comparisons in this respect. The comparison should rather be focused on the low percentage of cases finally included in Table 1 depending on the strict selection criteria. The absence of A cases of paracetamol may additionally be explained by the delay between intoxication and death. Because we excluded cases with longer survival time at hospitals, intoxications with acetaminophen and accompanying fatal liver necrosis will not appear in our presentation.

Table 3 also shows some interesting trends, for instance, the steady increase of the new antidepressants, particularly the selective serotonine reuptake inhibitors (SSRI), and the decrease of some other drugs. With some exceptions, the barbiturates were withdrawn from the Swedish market many years ago. This is why no barbiturates (apart from phenobarbital and thiopental) are presented in Table 1.

Every approach to the compilation of fatal and toxic drug concentrations is susceptible to some degree of circular reasoning. If such compilations were strictly followed and consistently used for the diagnosis of intoxications, further compilations would be meaningless. Thus, in clear-cut cases, the forensic pathologist and toxicologist should not shrink from an intoxication diagnosis even if the levels differ from those given in this and other compilations. In uncertain cases, on the other hand, in which the diagnosis is an open question, a reliable toxicology reference is a great help. Thus, we hope that this contribution will assist forensic pathologists and toxicologists in such situations. In particular, the presentation of drug concentrations of controls will hopefully give a more comprehensive view of fatal levels.

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9-76

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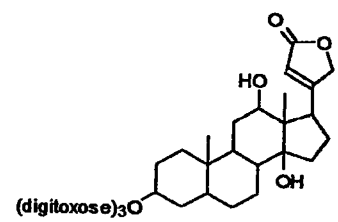
Digoxin



T½: 30–45 hr
Vd: 5.1–7.4 L/kg
Fb: 0.20

Occurrence and Usage. Digoxin (Lanoxin) is a cardiotonic plant glycoside that occurs in *Digitalis lanata* in combination with glucose and acetic acid. It is the 12-hydroxy analogue of digitoxin and is a major metabolite of that compound in man. In the treatment of congestive heart failure, digoxin is commonly given in daily oral maintenance doses of 0.25–0.75 mg; when initiating therapy, loading doses of 0.75–1.5 mg by intravenous or intramuscular injection or 2–3 mg orally may be administered. It is supplied in tablets of 0.125–0.5 mg and ampules containing 0.25 mg/mL.

Blood Concentrations. A single oral 0.25 mg digoxin dose administered to 6 fasting normal subjects resulted in serum concentrations that peaked at 1.13 μg/L at 1 hour and declined to 0.32 μg/L by 6 hours (Panisset et al., 1973). Peak plasma concentrations following a single 0.5 mg oral dose in 5 subjects averaged 1.4 μg/L at 2 hours on a full stomach, and 2.4 μg/L at 1 hour when fasting (White et al., 1971). Serum concentrations after a single intravenous 0.75 mg dose are initially as high as 13 μg/L at 10 minutes after injection but decline rapidly (Koup et al., 1975). Serum digoxin concentrations in 131 controlled patients receiving an average daily oral dose of 0.31 mg (range, 0.0625–1.0) averaged 1.4 μg/L (range, 0.3–3.0) (Smith and Haber, 1970). Blood for serum digoxin analysis should be drawn at least 6 hours after the last dose to avoid erroneously high values (Murphy et al., 1985).

Digoxin, unlike digitoxin, exhibits negligible binding to plasma proteins (Doherty et al., 1971) and distributes nearly equally between erythrocytes and plasma (Abshagen et al., 1971). The average elimination half-life in normal subjects is 37 hours (Huffman et al., 1974). The bioavailability of oral preparations ranges from 67% for tablets to 100% for an encapsulated elixir (Aronson, 1980). Recent data strongly suggests that digoxin follows nonlinear kinetics (Wagner et al., 1981).

Serum digoxin concentrations are effectively doubled during the co-administration of quinidine or quinine; this may result from a reduction in the binding of digoxin to skeletal muscle (Chen and Friedman, 1980; Leahey et al., 1980; Wandell et al., 1980; Schenck-Gustafsson et al., 1981).

Metabolism and Excretion. Digoxin is biotransformed to only a small degree in man. The metabolites are largely products of hydrolytic cleavage of the digitoxose group and of sulfate and glucuronide conjugation (Okita, 1964). An average of 59% of a single dose is excreted in the urine over

9-77

a 7 day period, of which 95–98% is unchanged drug; an average of 15% is excreted in the feces over the same period (Marcus et al., 1964; Doherty et al., 1970). In a 5 day period, 2% of a dose is eliminated as digoxigenin-bis-digitoxoside, 0.8% as digoxigenin-mono-digitoxoside, 0.3% as digoxigenin, and 0.3% as dihydrodigoxin (Gault et al., 1979). During chronic oral therapy, an average of 57% of a dose appears in the daily urine as apparently unchanged drug and urine concentrations are on the order of 25–125 μg/L (Huffman et al., 1974).

Myocardial/serum digoxin concentration ratios average 149 in infants and 28 in adults during therapy (Park et al., 1982). The following tissue distribution of the drug was determined from 17 adult patients who had been maintained on a mean daily dose of 0.005 mg/kg digoxin and who had not exhibited signs of toxicity prior to death (Andersson et al., 1975):

Digoxin Tissue Distribution During Therapy (μg/kg)*

	Brain	Atrial Myocardium	Ventricular Myocardium	Liver	Kidney	Skeletal Muscle	Fat
Average	32	65	133	72	128	30	10
(Range)	(3–74)	(27–129)	(50–296)	(29–186)	(56–253)	(13–56)	(4–23)

* By ^{86}Rb uptake inhibition after dichloromethane extraction

Toxicity. Digoxin toxicity is manifested by the same clinical signs as seen with digitoxin. Psychosis with vivid hallucinations has been described (Carney et al., 1985). Serum concentrations averaged 3.7 μg/L (range, 1.6–13.7) in 48 patients exhibiting toxic signs who were being maintained on a mean dose of 0.36 mg (range, 0.125–1.0) daily (Smith and Haber, 1970). A series of clinical reports of nonfatal and fatal digoxin poisoning have described cases of oral overdosage with 2.5–25 mg of the drug in which serum concentrations of 11–42 μg/L and elimination half-lives of 5–48 hours were observed (Smith and Willerson, 1971; Hobson and Zettner, 1973; Watanabe et al., 1977; Pearce et al., 1980). One subject who self-administered 200 mg of digoxin intravenously developed a maximum serum concentration of 52 μg/L after 4 hours and died after 6 hours (Reza et al., 1974). Antidotal treatment of a case of ingestion of 22.5 mg was successfully accomplished by the intravenous administration of digoxin-specific antibodies (Smith et al., 1976). Several authors have obtained benefit with charcoal hemoperfusion (Smiley et al., 1978; Marbury et al., 1979), while others do not recommend its use (Warren and Fanestil, 1979; Rowett, 1980); orally-administered charcoal has been reported to markedly shorten the elimination half-life (Boldy et al., 1985). Atropine and phenytoin have been found to completely reverse digoxin-induced arrhythmias (Ekins and Watanabe, 1978).

Reported postmortem blood concentrations for persons on therapy with digoxin vary considerably depending on the analytical method used and the anatomical origin of the blood specimen. Concentrations averaged 1.3 μg/L (range, 0.5–2.1) in 18 specimens of serum obtained from the right heart, but these values may be falsely low due to the effect of hemolysis on the ^{3}H-radioimmunoassay used (DiMaio et al., 1975). At the other end of the postmortem "therapeutic" range, Karjalainen et al. (1974) found an average of 4.6 μg/L (range, 1.3–8.2) in 13 samples of blood obtained from an unidentified source using an extraction-radioimmunoassay procedure. Probably the best defined study is that of Holt and Benstead (1975), who determined that complete hemolysis of a blood sample causes a decline of only 12% in the digoxin value relative to plasma; that serum taken from the right heart of 10 patients contained an average of 2.3 μg/L (range, 1.3–3.9) digoxin compared to an average of 1.4 μg/L (range, 0.7–2.9) in serum from the femoral vein of the same subjects; and that equivalent results were obtained for samples analyzed directly with either the ^{3}H or ^{125}I-radioimmunoassay, if correction for color quench was made when using the tritium label. It has been determined that serum digoxin levels nearly always increase after death due to leaching from muscle, with an average postmortem/antemortem ratio ranging from 1.42 for femoral vein blood specimens to 1.96 for heart blood specimens (Vorpahl and Coe, 1978). Fletcher et al. (1979)

suggested that postmortem blood samples for digoxin assay be taken from the peripheral circulation within a few hours after death, that they be completely hemolyzed by freezing and thawing several times, and centrifuged before analysis; the analytical value may then be multiplied by 1.3 to estimate the serum digoxin concentration at the moment of death.

At least 30 digoxin fatalities have been reported in which postmortem blood or serum concentrations were determined; the values range from 3.5–200 μg/L (average, 25) and represent both accidental and intentional overdoses (Iisalo and Nuutila, 1973; Moffat, 1974; Phillips, 1974a; DiMaio et al., 1975; Holt and Benstead, 1975; Ma, 1976; Dickson and Blazey, 1977; Selesky et al., 1977). In 2 digoxin fatalities, concentrations of 200 and 283 μg/L were measured in the left ventricular myocardium (Iisalo and Nuutila, 1973); these concentrations exceed the average therapeutic level for this tissue but are still within the normal range according to the above table. Aderjan et al. (1979) recommended that kidney concentrations be measured in the investigation of fatal digoxin poisoning, since this tissue appears to be dramatically elevated in such cases over normal values (140 ± 35 μg/kg). These authors found the following concentrations in a case of suicide by digoxin:

Digoxin Concentrations in a Fatal Case (μg/L or μg/kg)

Blood	Brain	Heart	Lung	Liver	Kidney
22	9.7	43	53	81	1400

Analysis. Digoxin has been successfully quantitated in body fluids by an ATP-ase inhibition technique (Burnett and Conklin, 1971) and by ^{86}Rb uptake inhibition assay (Gjerdrum, 1970). The latter method has been combined with solvent extraction in order to accommodate solid tissues (Andersson et al., 1975). The most frequently used technique for the determination of digoxin is radioimmunoassay (Smith et al., 1969). Certain of the commercially available radioimmunoassay systems are prone to errors from hemolysis, bilirubinemia or abnormal albumin levels (Cerceo and Elloso, 1972); removal of the digoxin from the specimen by extraction or dialysis improves the accuracy of the ^{3}H-radioimmunoassay (Phillips, 1974b), although the development of ^{125}I-systems has circumvented most of the problems associated with earlier assays. The commercial digoxin radioimmunoassay kits exhibit from 0.6–25% cross-reactivity with digitoxin, and many of the digoxin metabolites react to the same degree as digoxin itself (Stoll et al., 1972); on average, only 64% (range, 35–80) of serum digoxin as measured by radioimmunoassay is actually parent drug (Gault et al., 1984). Digoxin-like immunoreactivity has been reported present in the body fluids of individuals not receiving the drug (Balzan et al., 1984; Spiehler et al., 1985); this may be avoided by increasing incubation time during radioimmunoassay or by ultrafiltration of the specimen (Graves et al., 1986; Dasgupta et al., 1990). Thin-layer chromatography (Aderjan et al., 1979), liquid chromatography (Fletcher et al., 1980; Loo et al., 1981; Stone and Soldin, 1988) and solvent extraction (Picotte et al., 1991) have been used prior to immunoassay to provide additional specificity. Liquid chromatography with formation of a fluorescent derivative has been reported (Kwong and McErlane, 1986; Shepard et al., 1986).

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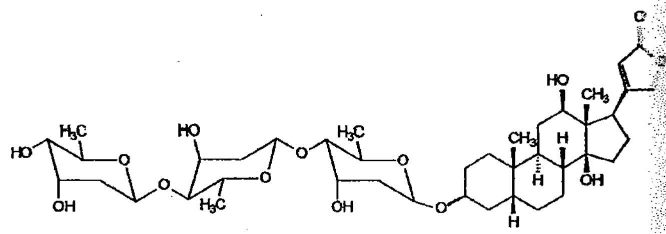
9-81

CHAPTER 122

Digoxin and Therapeutic Cardiac Glycosides

Kennon Heard



DIGOXIN

Molecular weight:	**Digoxin, 780.95 g/mol; digitoxin, 764.95 g/mol**
SI conversion:	**Digoxin, ng/ml × 1.28 = nmol/L; digitoxin, ng/ml × 1.31 = nmol/L**
Therapeutic levels:	**Digoxin, 0.8 to 2.0 ng/ml (serum); digitoxin, 15 to 25 ng/ml or higher (serum)**
Special concerns:	**Renal insufficiency or volume depletion may lead to occult chronic toxicity. Toxicity may develop with levels within therapeutic range.**
Target organs:	**Slowing or blocking of normal intracardiac conduction and increased atrial, nodal, and ventricular ectopy. Toxicity is manifested by a wide variety of dysrhythmias, most commonly bradycardia and conduction block.**
Antidote:	**Digoxin immune fragments (Fab)**

OVERVIEW

The cardiac glycosides are a diverse class of naturally occurring toxins that include digitalis, digitoxin, and structurally related plant and animal toxins. The cardiac glycosides consist of a steroid nucleus, an unsaturated lactone at the C-17 position, and a glucose moiety at the C-3 position (1). Two of these glycosides are currently used clinically: digoxin (Lanoxin, Lanoxicaps) and digitoxin (Crystodigin, Digicor, Digitaline). Digitalis and digitoxin are used for the treatment of congestive heart failure and for control of ventricular rate in atrial fibrillation and supraventricular tachycardia. Digitalis is the genus name for foxglove, and its leaf has been used therapeutically for more than 200 years. The extract of foxglove leaves contains several cardiac glycosides. Other sources of cardiac glycosides include oleander, red squill, yew berry, and *Bufo* toad poison (2–5). Plants containing cardiac glycosides are addressed in Chapter 306. Toxicity is most commonly a complication of chronic therapeutic use, but life-threatening toxicity after acute overdose also occurs.

Therapeutic Dose

The therapeutic dose of digoxin is 0.125 to 0.350 mg/day and is adjusted based on creatinine clearance (6). The therapeutic range of serum digoxin is 0.5 to 2.0 ng/ml (0.64 to 2.56 nmol/L). For digitoxin, the therapeutic dose is 0.05 to 0.30 mg/day, and the average serum level in patients without toxicity is 17 µg/L, with a range of 3 to 39 µg/L (7).

Toxic Dose

The estimated adult toxic dose after acute ingestion is 10 mg (8). Case reports suggest that toxicity from acute overdose typically occurs with serum levels above 10 ng/ml (12.8 nmol/L). A 32-year-old woman on chronic digoxin therapy developed vomiting and ventricular ectopy after ingestion of 1.75 mg of digoxin in a suicidal gesture (9). A 19-year-old woman died after ingestion of 440 µg/kg of digoxin and 1300 mg of propoxyphene (10). A 60-year-old woman with a history of moderate heart failure on chronic digoxin therapy died after acute ingestion of 10 mg of digoxin (11).

Children are generally more resistant to the effects of cardiac glycosides. Nevertheless, pediatric deaths after accidental ingestion and therapeutic errors are well described. Serious toxic effects are likely after ingestion of more than 0.1 mg/kg of digoxin (12). Death has been reported after ingestion of 10 mg in a 19-month-old child, although the management of digoxin poisoning has changed substantially since this case was reported in 1964 (13). A 2.5-year-old child developed ventricular fibrillation after ingestion of [illegible] mg but survived with digoxin immune Fab therapy (14).

TOXICOKINETICS AND TOXICODYNAMICS

Digoxin is concentrated in tissue (primarily skeletal muscle) and therefore has a large volume of distribution (Table 1). The volume of distribution is decreased in obese individuals and in the elderly due to loss of muscle mass, and interpatient variation is high. Time to onset of action is 0.5 to 2.0 hours for oral digoxin formulations, and peak effects are noted in 2 to 6 hours. Intravenous (IV) preparations have an onset of action within minutes and peak effects occur in 1 to 4 hours (6). Digoxin is excreted unchanged by the kidneys (15). Unrecognized impaired renal function is one of the most common reasons for toxicity during chronic use. The elimination half-life for therapeutic levels in patients with normal renal function is 30 to 45 hours (15). Dig-

TABLE 1. Pharmacokinetic and pharmacodynamic data for digoxin and digitoxin

Parameter (reference)	*Digoxin*	*Digitoxin*
Bioavailability (%) (6,15)	*Lanoxicaps: 90–100; others: 60–85*	*Nearly 100*
Maximal drug concentration (7,15)	0.25 mg PO: mean level of 1.13 μg/L at 60 min	0.6 mg IV: mean level of 51 μg/L at 2–5 min
Time of maximal concentration (h) (15,82)	1.5–6.0	1–2
Volume of distribution (L/kg) (7,83)	Newborn: 5–10; infant: 8–16; children: 8.6–12.0; adults: 5.0–7.5	41
Route of excretion (7,15)	Renal	Hepatic
Elimination half-life (7,15)	30–45 h	4–7 d
Protein binding (%) (7,15)	20–30	97

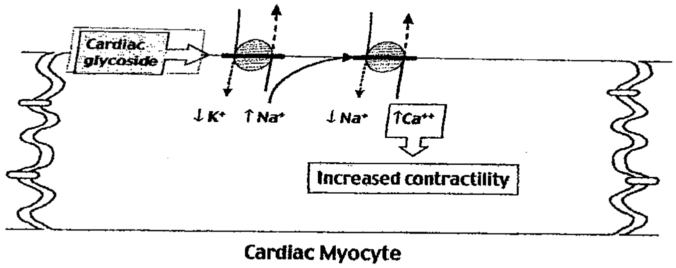


Figure 1. Mechanism of cardiac glycoside activity on the cardiac myocyte. Cardiac glycosides decrease the activity of the sodium-potassium pump. The resulting increase in sodium within the cell reduces influx of extracellular sodium. The decreased influx reduces the activity of the sodium-calcium antiport pump and thereby increases the amount of calcium within the cell. The increased calcium concentration increases the interaction of actin and myosin and produces increased contractility in failing heart cells.

Digitoxin is extensively metabolized by the liver, primarily excreted in bile (60% to 70%) and has an elimination half-life of 4 to 7 days (7). Its primary metabolite is digoxin.

Some toxicokinetic aspects of digoxin are known. In children, the serum concentration may continue to rise well after administration has stopped (16). The volume of distribution decreases as serum concentration rises. In overdose, the elimination half-life of digoxin is reported to increase or decrease. Most reports indicate an increase in half-life.

Serum digoxin levels increase after death. In a pediatric study, digoxin levels in the first 24 hours after death averaged 5.1 ng/ml (6.5 nmol/L) higher than calculated digoxin levels at the time of death (17). Other reports have also noted markedly elevated postmortem levels (18).

PATHOPHYSIOLOGY

Cardiac glycosides have two effects that are responsible for both therapeutic and toxic effects. The first effect is inactivation of the sodium potassium–adenosine triphosphate dependent pump (Na^+,K^+-adenosine triphosphatase) on the cytoplasmic membrane of cardiac cells. The Na^+,K^+-adenosine triphosphatase exchanges extracellular potassium for intracellular sodium. After inactivation of this pump, the concentration of intracellular sodium increases, leading to decreased activity of the Na^+-Ca^{2+} antiport pump (Fig. 1). The Na^+-Ca^{2+} pump exchanges extracellular sodium for intracellular calcium; therefore, the elevation of intracellular calcium increases myocardial contractility. The elevation of intracellular calcium concentration also raises the resting membrane potential of the cell, which increases the rate of spontaneous cellular depolarization and increases myocardial automaticity (1). This effect is most pronounced in atrial tissue, the atrioventricular (AV) node, the His-Purkinje system, and in ventricular tissue (19).

The impaired sodium-potassium exchange also causes the serum potassium level to rise because potassium is moved intracellularly at a slower rate (Fig. 1). After acute poisoning with a cardiac glycoside, the serum potassium may become dangerously high (20). Interestingly, an elevated serum potassium level is actually protective in the setting of chronic digoxin toxicity because hypokalemia increases glycoside binding to the Na-K pump and worsens poisoning of the pump (1). Therefore, a temporary elevation of serum potassium is acceptable in the setting of chronic digoxin toxicity but not in the setting of acute digoxin toxicity.

A second major effect of cardiac glycosides involves the cardiac autonomic system. Digoxin increases cardiac vagal tone and decreases sympathetic nervous system activity in cardiac tissue. This prolongs the refractory period of the conducting system, decreases sinus node firing, and slows conduction through the AV node (1). In overdose, this may lead to sinus bradycardia, sinus arrest, or varying degrees of AV heart block.

The overall effect of cardiac glycoside poisoning is a combination of slowing or blocking of normal intracardiac conduction and increased atrial, nodal, and ventricular ectopy.

PREGNANCY AND LACTATION

Digoxin is U.S. Food and Drug Administration pregnancy category C (Appendix I). Digoxin is excreted in breast milk but is not contraindicated because the concentrations achieved do not cause toxicity in infants (6).

CLINICAL PRESENTATION

Acute and Subacute Overdosage

Acute toxicity most commonly follows suicidal overdose but may occur after accidental ingestion of medications or plants (Chapter 255). The primary manifestations of acute toxicity include vomiting, bradycardia, heart block, ventricular dysrhythmias, and hyperkalemia (10,21,22).

A large case series of acute digitoxin overdose reported 13% mortality with supportive treatment, including intracardiac pacing (21). Although prospective data are limited, it is likely that digoxin immune +Fab (DFab) therapy has improved survival (23). For example, survival of patients with cardiac arrest from digoxin poisoning when treated with DFab was 46%, whereas mortality before this treatment approached 100% (24).

Toxicity during Chronic Use

In older studies, up to 30% of admitted patients taking digoxin had evidence of digoxin toxicity (25). More recent studies suggest that the incidence in admitted patients and outpatients is much lower (26,27). In fact, one study reported that 20% of patients with a discharge diagnosis of digoxin poisoning had no clinical evidence of digoxin toxicity (26). Similarly, older studies suggested that mortality of patients with definite digoxin intoxication exceeded 40% (25), whereas more recent studies suggest mortality is less than 5% (26).

9-83

TABLE 2. Drugs that increase serum digoxin levels

Alprazolam	Propafenone
Amiodarone	Quinidine
Indomethacin	Spironolactone
Itraconazole	Tetracycline
Macrolide antibiotics	Verapamil

Adapted from Lanoxin. In: *Physicians' Desk Reference*, 54th ed. Oradell, NJ: Medical Economics, 2000:1225–1231.

The most clinically significant manifestations of chronic cardiac glycoside toxicity are ventricular irritability, including ventricular ectopy, bigeminy, or trigeminy, and ventricular tachycardia (22). AV block and AV nodal escape rhythms are also common (22). Gastrointestinal symptoms, such as anorexia, nausea, and vomiting, occur in approximately one-half of patients (25,28). Alteration in mental status was reported in 25% of patients (25,29). General malaise and weakness are also common and may be the most prominent symptoms (25). Visual changes, such as halos, altered color perceptions, or clouding of vision, are common. Most series report visual symptoms in 10% to 20% of toxic patients (30), but one series has reported symptoms in 95% of patients with digitoxin toxicity (31). Formal testing detected color vision alteration in 80% of digoxin-toxic patients (32).

There are three common reasons for chronic digoxin toxicity. One is alteration of the digoxin dose, either by the patient or by the caregiver. The second is alteration in digoxin clearance, most commonly by unrecognized decreased renal function. The final cause is interaction with other drugs (Table 2).

Adverse Reactions

Adverse reactions are most commonly toxic effects as described in the section Clinical Presentation: Toxicity during Chronic Use. Various psychiatric complaints, including headache, fatigue, malaise, stupor, and mild encephalopathy with electroencephalogram changes, have been described. These effects are typically associated with serum levels in the toxic range. Gynecomastia, rash, and thrombocytopenia have been noted with chronic use (6).

DIAGNOSTIC TESTS

Acute and Subacute Overdosage

An elevated serum digoxin level in the presence of toxic effects establishes the diagnosis of acute or subacute digoxin toxicity. Serum digoxin levels are commonly available and should be obtained for evaluation of acute overdose in adults and children; however, they must be interpreted carefully. Very high serum levels (greater than 10 ng/ml, 12.8 nmol/L) may be noted after acute ingestion in otherwise minimally symptomatic patients (33,34). The serum level should be drawn at least 6 hours after ingestion. Very high levels in asymptomatic patients may also occur when the measurement is performed before distribution has occurred (i.e., after IV administration). A level more than 6 hours after ingestion often is normal in these cases.

Current immunoassays for digoxin may cross-react to variable degrees with other cardiac glycosides (2,35). A positive digoxin screen in a patient with a history of ingesting cardiac glycoside helps to confirm the ingestion; however, a negative test does not exclude ingestion. One report suggests that there is a correlation between serum digoxin levels and oleandrin (the primary toxic component of oleander) levels after ingestion of pink oleander, but there is likely variation depending on the assay (36). High-performance liquid chromatography may be used to measure serum oleandrin levels (37,38).

Falsely low serum digoxin levels may be noted in patients being treated with spironolactone or canrenone (39). Newborns, pregnant women, and patients with end-stage liver disease, end-stage kidney disease, or hypothermia may have increased serum digoxin levels without toxic effect. The increased level is caused by an endogenous digoxin-like immunoreactive substance that reacts in the digoxin immunoassay (40–43).

Serum potassium is the best predictor of cardiac glycoside toxicity after acute overdose. In one large study of acute digoxin ingestion, all patients with a serum potassium level greater than 5.5 mEq/L died, whereas no patient with a serum level less than 5 mEq/L died (20). This rule is not completely reliable in clinical practice, but elevated serum potassium levels should be addressed promptly. Serum potassium has also been suggested as a useful marker of severe toxicity in toad-toxin poisoning ([illegible]).

Renal function should be evaluated because renal insufficiency has been associated with recurrent digoxin toxicity after DFab therapy (45).

The electrocardiogram is used to assess cardiac conduction effects of cardiac glycosides and to help guide therapy. Common findings include bradycardia, junctional rhythms, varying degrees of AV block, and ventricular ectopy (21).

Toxicity during Chronic Use

The serum digoxin level correlates poorly with toxicity (46,47). One older study suggested that 30% of clinically toxic patients had serum levels less than 1.7 ng/ml (48,49). A more recent study noted that many patients with toxic effects had a serum level between 1 and 2 ng/ml (26). The diagnosis of digoxin toxicity is primarily a clinical diagnosis, and only very low serum levels are helpful in excluding the diagnosis.

In addition to measurement of the serum digoxin level, serum potassium, magnesium, urea nitrogen, and creatinine should be determined. Hypokalemia and hypomagnesemia are associated with increased dysrhythmias in patients with chronic digoxin toxicity (25,47). Renal function should be determined as many cases of chronic toxicity are associated with decreased renal clearance. Furthermore, renal insufficiency may decrease clearance of the digoxin-DFab complex, which may result in recurrent toxicity after DFab treatment (45).

An electrocardiogram should be obtained and continuous cardiac monitoring initiated in all patients with suspected cardiac glycoside toxicity. Signs of myocardial irritability, such as atrial or ventricular ectopy or tachycardia, are the most common manifestations of chronic toxicity. Sinoatrial or AV blocks are also common but less so than with acute toxicity. The combination of a supraventricular tachycardia with AV block or atrial fibrillation with a nodal escape rhythm is highly suggestive of chronic digoxin toxicity (50). Other tests to evaluate the suicidal patient should be considered.

Diagnostic Pitfalls

The most common pitfall in the evaluation of possible cardiac glycoside toxicity is over-reliance on the serum digoxin level. As noted above, levels drawn before steady-state conditions after acute ingestion may be markedly elevated but result in relatively minimal toxicity (34). In contrast, patients on chronic digoxin therapy may have life-threatening toxicity with "therapeutic" serum levels.

TREATMENT

The principle of management is to treat life-threatening effects (hyperkalemia, ventricular dysrhythmia) immediately, then reduce further absorption of the drug, and finally provide meticulous supportive care during recovery. Digoxin immune antibody fragments (DFab) (DigiBind, DigiFab) have revolutionized the treatment of cardiac glycoside toxicity. Any patient with life-threatening symptoms or ingestion of a potentially life-threatening dose should be treated in a facility that has an adequate dose of DFab immediately available. Suicidal ingestion of cardiac glycoside medication should be considered life-threatening. Accidental ingestion of cardiac glycoside medication may be life-threatening, but accidental ingestion of plants that contain cardiac glycosides is rarely life-threatening.

Gastrointestinal Decontamination

Emesis is not recommended for cardiac glycoside medication ingestion, although induced emesis has theoretic usefulness in the case of deliberate ingestion of cardiac glycoside–containing plants if spontaneous vomiting has not occurred. Cardiac glycosides are well adsorbed by charcoal. Administration of charcoal should be considered in all cases that present within 1 to 2 hours of ingestion (51). There are no data to support routine administration of a cathartic with charcoal in cardiac glycoside ingestion. Similarly, there are no available data to evaluate whole bowel irrigation after cardiac glycoside ingestion, although it has theoretic usefulness in the case of deliberate plant ingestion.

Enhancement of Elimination

Multiple-dose activated charcoal is not clearly beneficial in digoxin overdose (52). Multiple-dose activated charcoal increases the clearance of digitoxin. Given the prolonged half-life of digitoxin, multiple-dose activated charcoal should be considered after digitoxin overdose (53). Hemoperfusion increases the clearance of digitoxin but is rarely used given the efficacy of digoxin immune antibody fragments. Hemodialysis and peritoneal dialysis do not increase the clearance of digoxin and are not considered clinically useful (54). Furthermore, these treatments do not appear to increase the clearance of digoxin bound to DFab (54).

Antidotes

Digoxin immune antibody fragments (DFab) were developed for the treatment of cardiac glycoside toxicity in the 1970s (Chapter 49). DFab rapidly reverses the cardiac effects of digitalis, digitoxin, oleander, yew berry, and bufotoxin, particularly in the case of acute poisoning (2,3,24,35,55). A randomized, controlled trial demonstrated effective reversal of bradycardia and hyperkalemia in patients with cardiac glycoside poisoning from yellow oleander ingestion (56). *In vitro* studies suggest DFab also binds other plant-derived cardiac glycosides (57). Effects are generally observed within 1 hour of DFab administration, and complete reversal is expected within 4 to 6 hours of administration (24). The effects of acute poisoning often reverse quickly, whereas chronic ingestion often improves slowly and partially. The beneficial effect in chronic poisoning may be difficult to ascertain because of preexisting cardiac disease.

Widely accepted indications for administration of DFab after acute digoxin ingestion include any dysrhythmia that results in hemodynamic compromise or a serum potassium level above 5 mEq/L (19). Administration is also recommended after acute ingestion of more than 4 mg in a previously healthy child and 10 mg in a previously healthy adult (8). Finally, administration is recommended if the steady-state serum digoxin level is greater than 10 ng/ml (12.8 nmol/L) (8).

The appropriate dose of DFab after acute digoxin overdose is not well established. Adult patients with hemodynamic compromise after acute cardiac glycoside ingestion should be treated with 10 to 20 vials (380 to 760 mg). Stable patients may be treated with dosing based on the ingested amount (if known) or on the steady-state serum level.

If only the amount ingested is known (Eq. 1):

$$\text{number of DFab vials} = \text{amount of digoxin ingested (mg)} \times 0.48\ \text{(mg/vial)} \qquad \text{[Eq. 1]}$$

If the serum digoxin level obtained at least 6 hours after ingestion is known (Eq. 2):

$$\begin{array}{c}\text{number}\\ \text{of DFab vials}\end{array} = \frac{\begin{array}{c}\text{serum digoxin}\\ \text{level (ng/ml)}\end{array} \times \text{ideal body weight (kg)}}{100} \qquad \text{[Eq.2]}$$

It is important to note that calculating the dose of DFab using a serum level drawn before steady-state is reached (at least 6 hours after ingestion) may result in administration of a large, expensive, and unnecessary excess of DFab (34).

Patients who develop cardiac toxicity during chronic digoxin therapy usually require much less DFab than those with acute intoxication. Chronic ingestion usually requires less than five vials, whereas toxicity after acute ingestion requires more—up to 10 or 20 vials in patients with hemodynamic compromise. When a steady-state serum level is known, Equation 2 may be used to determine the dose of DFab. An alternative for stable patients with chronic poisoning is to administer two to four vials of DFab and then repeat the dose based on patient response.

Some clinicians have used an approach intended to leave some unbound digoxin present in the blood in order to maintain the desired digoxin activity. This can be accomplished theoretically using Equation 2 by substituting [serum digoxin level (ng/ml) – 1] to maintain a free digoxin level of 1 ng/ml. However, binding varies among patients, and the digoxin level varies depending on the time of serum sampling; therefore, deliberate partial reversal of patients (to maintain a therapeutic digoxin level) is likely inaccurate and cannot be recommended.

DFab is provided as a lyophilized powder. Each vial is reconstituted in 4 cc of sterile water and then may be diluted to the desired final volume in 5% dextrose or normal saline. During reconstitution the solution should be gently rolled rather than shaken to prevent foaming. DFab is administered to stable patients over 30 minutes through a 0.22 μm filter. It may be administered as a bolus to patients with hemodynamic compromise or cardiac arrest (8).

Adverse effects during or after DFab administration are rare. Because DFab is derived from animal protein, allergic reactions are the primary concern. A history of allergy to sheep products has been considered a relative contraindication to administration. No serious allergic reactions were reported in the largest multicenter study of DFab (24). A postmarketing surveillance study reported six cases of possible adverse reactions, none of which were serious (22). Patients with a history of asthma or allergy to antibiotics were found to have an increased risk of allergic reactions. Repeat DFab treatment after repeat overdose without allergic reaction has been reported (58). Other effects reported include hypokalemia (common), worsening of heart failure, and loss of ventricular rate control (rare) (24).

Atropine is a secondary antidote. Although atropine is often ineffective, several case reports and series have reported reversal of bradycardia from acute digoxin poisoning after atropine adminis-

9-85

tration (10,59–62). In the setting of acute overdose, adverse effects appear to be unusual. There are some reported cases of adverse effects of atropine when given to patients with chronic digoxin toxicity (63). Atropine should be considered standard therapy (while preparing DFab for administration) for symptomatic bradycardia associated with acute digoxin overdose. The adult dose is 0.5 to 1.0 mg IV and repeated every few minutes until the heart rate increases, up to a total dose of 3 mg. The pediatric dose is 0.01 mg/kg.

Phenytoin was once considered the first-line treatment for ventricular dysrhythmias associated with digoxin toxicity. Two older case series reported successful treatment of ventricular dysrhythmias using phenytoin, although many of these patients demonstrated only ventricular ectopy. One of these series also reported successful treatment in seven of eight patients with supraventricular tachycardia. The doses used in these reports were 100 to 350 mg administered as an IV bolus (64,65). One case reported successful treatment of a patient with bradycardia and heart-block after acute overdose with repeated 25-mg IV boluses (66). Phenytoin should be administered as an IV bolus of 100 to 300 mg to patients with ventricular dysrhythmias from digoxin poisoning when DFab is not available.

Magnesium has been used for the treatment of ventricular ectopy, dysrhythmias, and cardiac arrest in the setting of chronic digoxin toxicity (67,68). The pretreatment serum magnesium levels in these case series were not reported. Successful defibrillation has been reported after magnesium administration in a case of acute digoxin overdose that did not respond to lidocaine and phenytoin (69). A case of successful magnesium therapy for ventricular dysrhythmias in a patient with acute on chronic toxicity has also been reported (70). No serious adverse effects have been reported commonly. Based on these limited data, IV administration of 2 to 4 g of magnesium sulfate appears to be helpful in the treatment of ventricular ectopy and dysrhythmias in patients with digoxin toxicity if DFab is not available. The effects are often transient, and the dose may need to be repeated.

Lidocaine is commonly recommended for digoxin-induced ventricular dysrhythmias. In one case series of eight digoxin-toxic patients with bidirectional ventricular tachycardia, seven were successfully converted to an atrial rhythm within 2.5 hours (71). The dose was two 75-mg boluses followed by a 3-mg/minute infusion. The one patient who did not respond developed ventricular fibrillation 5 minutes after the first dose. Another report noted asystole after lidocaine administration for ventricular dysrhythmias in a digoxin-toxic patient (72). Overall, the data to support the use of lidocaine for ventricular dysrhythmias associated with digoxin toxicity are limited.

Amiodarone has been used successfully to treat ventricular fibrillation in two cases of digoxin poisoning (one case in conjunction with DFab) (73,74).

Prophylactic intracardiac pacing was initially recommended (before introduction of DFab) for patients with acute digoxin ingestion and either dysrhythmias plus delayed intracardiac conduction or serum potassium over 5 mEq/L. Other indications were subsequently added: age greater than 40 years, digitoxin dose greater than 10 mg, and severe vomiting or previous organic heart disease (21). The pacer was activated for severe AV block or for ventricular ectopy. The pacer voltage is set for twice the excitability threshold, and the rate increased until ectopy resolves. Later work from this same center has demonstrated improved survival after DFab therapy compared to pacing (23). If DFab is not available, however, transvenous pacing should be instituted for patients with these indications. Transcutaneous pacing has also been used successfully during resuscitation of a patient with acute glycoside poisoning (3).

Ventricular fibrillation after cardioversion has been reported in two digoxin-toxic patients soon after electrical cardioversion introduced for tachydysrhythmias (75). Animal studies indicate that supratherapeutic digoxin doses increase the duration of ventricular tachycardia (76) and decrease the ventricular fibrillation threshold (77). Furthermore, digoxin-toxic animals that develop ventricular tachycardia or fibrillation are often recalcitrant to defibrillation (76). Overall, stepwise escalation of the energy used for cardioversion, beginning at 10 J and increasing as needed, should be used with the stable digoxin-toxic patient who requires cardioversion (75). Unstable patients may benefit from treatment with an antidysrhythmic agent before cardioversion or defibrillation, but information is limited. Patients with therapeutic digoxin levels do not appear to be at increased risk of postcardioversion dysrhythmias (78).

Potassium should be administered to patients with chronic digoxin poisoning with hypokalemia. Older studies recommend oral salt administration, although cautious IV administration may be used as well. Because hyperkalemia is a consequence of acute digoxin poisoning, potassium should not be administered after acute digoxin toxicity. After acute poisoning, DFab is considered first-line therapy for hyperkalemia. If DFab is not available, standard therapy for hyperkalemia should be used, with the exception of calcium administration. Calcium is not recommended for treatment of hyperkalemia associated with digoxin poisoning (79).

Historically, calcium disodium edetate was reported to suppress ventricular ectopy and tachycardia in the treatment of chronic digoxin toxicity, presumably due to the resultant hypocalcemia (80). However, this therapy is not currently used nor recommended.

Monitoring

The patient's vital signs, electrocardiogram, and cardiac rhythm should be monitored, usually in the intensive care unit. After administration of DFab, serum digoxin levels are often unreliable and require specific serum separation techniques to obtain meaningful results (81). Serum potassium level often falls with DFab therapy, and mild to moderate hypokalemia has been noted after DFab therapy (24).

Supportive Care

Patients with altered mental status should have early airway management and appropriate evaluation for coingestants and other causes of altered mental status. Hypotension should be treated with isotonic crystalloid fluids, DFab administration, and vasopressors, if needed. Because patients on chronic glycoside therapy have cardiac disease, patients should be monitored closely for cardiac ischemia and infarction. Patients with evidence of dehydration should receive adequate fluid resuscitation and evaluation for an underlying cause of dehydration (i.e., overuse of diuretics or underlying illness, resulting in decreased fluid intake).

Patients with typical acute toxicity present with gastrointestinal symptoms and bradycardia. However, as life-threatening effects may occur with ingestion of less than a 1-month supply of medications, patients with deliberate ingestions should be treated in a critical care setting with DFab immediately available.

Patients with chronic digoxin toxicity often present with bradycardia associated with nonspecific effects that are not life-threatening. Patients often are dehydrated, and this results in prerenal azotemia and glycoside accumulation. These patients generally do well with gentle hydration and monitoring.

As the toxic effects of digoxin are often nonspecific in older patients, the diagnosis of chronic digoxin toxicity should be entertained for older patients taking digoxin who present with an unclear etiology of their symptoms.

Management Pitfalls

The development of DFab has dramatically simplified the management of the patient with cardiac glycoside toxicity. Once the clinician determines that significant toxicity exists or is likely to occur, DFab should be administered. The most significant pitfall is failure to recognize that serious toxicity exists or will soon develop. For example, hyperkalemia may be treated without recognizing that the underlying cause is cardiac glycoside poisoning. In addition, a high-normal or elevated potassium level may not be assessed correctly in patients on chronic digoxin treatment.

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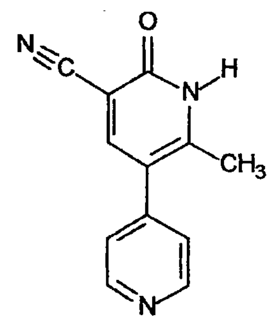
CHAPTER 123

Phosphodiesterase Inhibitors

Andrew R. Erdman



<u>**MILRINONE**</u>

Compounds included:	**Inamrinone (Inocor), milrinone (Primacor)**
Molecular formula and weight:	**Inamrinone ($C_{10}H_9N_3O,C_3H_6O_3$), 187.2 g/mol; milrinone ($C_{12}H_9N_3O$), 211.2 g/mol**
SI conversion:	**Inamrinone, mg/ml x 5.34 = mml/L; milrinone, mg/ml x 4.73 = mmol/L**
CAS Registry No.:	**75898-90-7 (inamrinone); 78415-72-2 (milrinone)**
Therapeutic levels:	**Inamrinone, 2 to 7 mg/ml (serum)**
Special concerns:	**Hypotension, tachycardia**
Antidote:	**None**

OVERVIEW

Phosphodiesterase (PDE) is a common intracellular enzyme found in a variety of organs and tissues within the human body (1,2). It catalyzes the cytosolic breakdown of cyclic adenosine monophosphate (cAMP) and other cyclic nucleotides, which are common second messengers and potent modulators of cellular function. PDE has several different forms or isoenzymes, distinguished by their organ location and by the specific cyclic nucleotide used as a substrate. The PDE inhibitors are a diverse group of agents that have found a wide range of clinical applications in modern medicine. Most PDE inhibitors are specific for a particular PDE isoenzyme. For example, the methylxanthines, such as theophylline and aminophylline, inhibit primarily PDE 4, whereas sildenafil inhibits primarily PDE 5. This chapter focuses on drugs that inhibit PDE 3, inamrinone and milrinone.

Inamrinone and milrinone are bipyridine molecules that inhibit PDE, with particular specificity for the PDE 3 isoenzyme found in cardiac myocytes and vascular smooth muscle (1–5). This results clinically in improved cardiac contractility and peripheral vasodilation (6–14). Secondary effects include the inhibition of platelet aggregation and immunomodulation (13,15–19). Overdoses, although not well reported, may lead to an extension of the drugs' clinical effects, with excessive vasodilation causing hypotension and reflex tachycardia.

Inamrinone was the first PDE 3–specific inhibitor (20,21). It was originally called *amrinone* but was renamed due to name confusion with the drug amiodarone. Intravenous (IV) inamrinone is

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Arch. Toxicol. 42, 107–114 (1979)

Archives of TOXICOLOGY

Investigation of Cardiac Glycoside Levels in Human Post Mortem Blood and Tissues Determined by a Special Radioimmunoassay Procedure*

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Abstract. Even after the introduction of radioimmunological methods the question of a cardiac glycoside causing or contributing to the death of a patient can not be answered satisfactorily. By means of a special radioimmunoassay procedure for digoxin as well as for the structurally related methyl- and acetylderivatives we measured the concentrations in human blood and post mortem tissues.

We investigated the glycoside contents in the blood of intravenously digitalised (Novodigal®) patients before and after death. At autopsy blood specimens were taken from the heart and the femoral vein. We found an increase of the glycoside level up to a highly toxic range (7–15 ng/ml) especially in the heart blood. Thus post mortem blood levels of digoxin and its derivatives are not suitable for a final decision in alleged cases of fatal poisonings.

Measuring various concentrations in tissues and body fluids of the above cardiac glycosides mentioned revealed the kidney concentration to be of high value in confirming a digitalis poisoning. This organ and the heart show the highest tissue concentrations. Interpretations of fatal digitalis poisonings should be based on the additional knowledge of these concentrations. Individual cardiac glycosides may be analyzed by a combination of thin layer chromatography and radioimmunoassay.

Key words: Digoxinpoisoning — Blood levels — Tissue concentrations — Radioimmunoassay — Thin layer chromatography.

Zusammenfassung. Selbst nach der Einführung von radioimmunologischen Methoden kann die Frage, ob ein Herzglykosid einen Tod verursacht hat oder zumindest dazu beigetragen hat, nicht zufriedenstellend beantwortet werden. Mit Hilfe eines besonderen Radioimmunoassay-Verfahrens für Digoxin, welches auch für die strukturell verwandten Methyl- und Acetyl-Derivate anwendbar ist, haben wir post mortem-Konzentrationen dieser Stoffe im menschlichen Blut und

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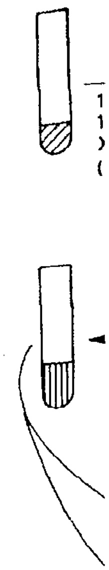
Gewebe untersucht. Die Glykosid-Spiegel von intravenös digitalisierten (Novodigal®) Patienten können nach dem Tod bis in einen 2,5fach höheren Bereich ansteigen (7–15 ng/ml im Herzblut), verglichen mit den Glykosid-Spiegeln vor dem Tod. Da so eine starke Toxizität der Blutspiegelhöhe vorgetäuscht wird, sind nach dem Tod Blutspiegelmessungen allein für die Beurteilung von vermuteten Digitalis-Vergiftungen nicht ausreichend.

Bei der Messung von Glykosidkonzentrationen in Geweben und Körperflüssigkeiten ist der Konzentration in Herz und Niere besondere Beachtung zu schenken, diese beiden Organe zeigen die höchsten Gewebskonzentrationen. Eine Beurteilung sollte Konzentrationsmessungen in diesen Organen berücksichtigen. Mittels einer kombinierten dünnschichtchromatographischen und radioimmunologischen Analyse ist es möglich, die Identität von zur Anwendung gelangten Herzglykosiden im ng-Bereich festzustellen.

Schlüsselwörter: Digoxin-Derivate – Vergiftung – Gewebskonzentrationen – Radioimmunoassay – Dünnschichtchromatographische Analyse.



Introduction

Frequent radioimmunological monitoring has proven useful in the medication of digoxin and its commonly used derivatives. The optimal use of cardiac glycosides and prevention of toxic complications need thorough knowledge of their potency, of individual changes of pharmacokinetics and of factors influencing the individual tolerance like body weight, drug interactions, electrolytes and renal function.

An optimal therapeutic response is obtained at serum levels between 1.2 and 1.7 ng digoxin equivalents/ml (Haasis and Larbig, 1975; Schneider and Ruiz-Torres, 1977) patients show toxic symptoms with a mean serum level of 3.1 ng/ml and digoxin levels of more than 7 ng/ml are reported to be indicative of a fatal overdose (Moffat, 1974). Nevertheless mortality in patients who develop digitalis intoxication during therapy has been between 7 and 25% (Beller et al., 1972; Hennersdorf, 1976).

To the forensic toxicologists however an answer to the question whether a cardiac glycoside has contributed to the death of a patient still seems to be a matter of opinion.

We have carried out own measurements after developing a special radioimmunoassay (RIA) procedure. In this paper we report our experiences with this technique applied to post mortem specimens.

Material and Methods

Blood samples of eight patients were taken from intravenously digitalised (Novodigal®) patients before and within 30 min after death. At autopsy the corresponding blood specimens were collected from the heart (left ventricle) and from the femoral vein. Tissue samples of normally digitalised patients were taken at autopsy as well as tissue materials from a suicidal case. The blood samples were extracted using an Amberlite XAD-2 resin. The technique is described in Figure 1. An important purification step is the combined desorption/solvent partition using 5% ammonia solution and ethylacetate. A reproducible recovery of 70.6 ± 2.3 is obtained using ^{3}H-Digoxin as a tracer.

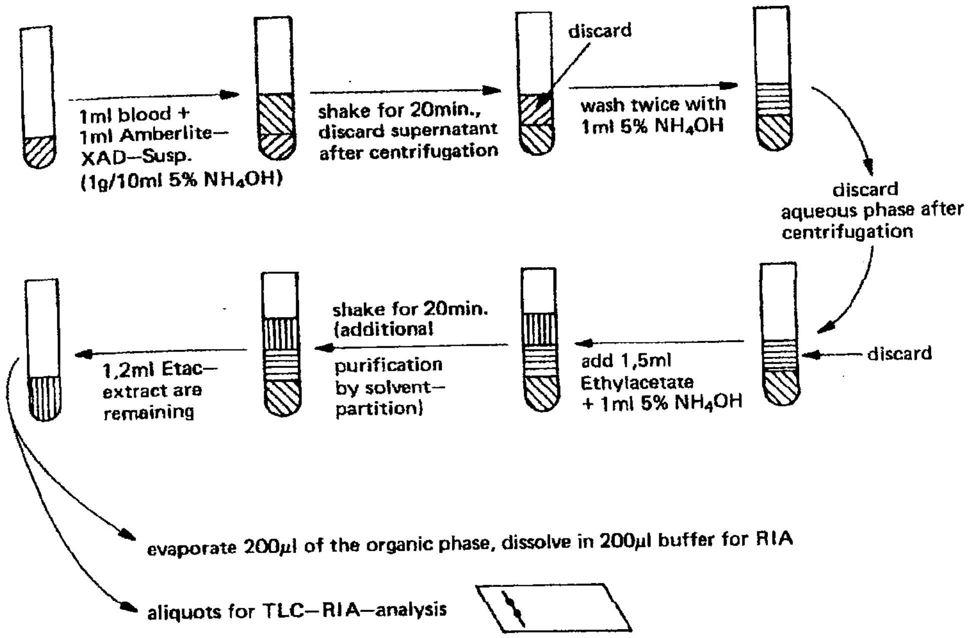


Fig. 1. Extraction of cardiac glycosides from post mortem blood by Amberlite-XAD-2

Tissue samples of 0.5 g wet weight were lyophilized prior to organic solvent extraction with methanol and reconstitution of the original concentration by assay buffer.

The assay was performed with anti digoxin antisera and ^3H-digoxin commercially available (New England Nuclear, Dreieichenhain, GFR). Buffers and separation methods are previously described (Will et al., 1977). The coeffients of intra- and inter assay variation was 7.1 ± 2.5 and 10.2 ± 4.6 respectively. The calibration curves were produced by extracting standard digoxin concentrations of 0.5–16 ng/ml from drug free blood. The antisera were tested for the individual *cross reaction* characteristics of digoxin metabolites. Corrected for molecular weight the bis- and monodigitoxides as well as the digoxigenin crossreacted by 100%. This was also found in a detailed crossreaction study for anti digoxin antisera by Flasch et al. (1977). A thinlayer chromatographic analysis by radioimmunoassay detection was accomplished by the use of TLC-plastic sheets (Silicagel 60 F_{254}, Merck, Darmstadt, GFR).

The solvent system consisted in chloroform/ethanol 95 : 5. The distance between start and solvent front was divided into 5 mm zones which were cut off for desorption with H_2O/ethylacetate (1 : 1). The partition between water and ethylacetate turned out to be an important purification step. The organic phase was evaporated and the residue was dissolved in a corresponding volume of assay buffer. Aliquots were taken for the radioimmunoassay.

Results and Discussion

Ante- and Post Mortem Blood Levels

With the technique described we investigated the digoxin blood levels in patients with terminal illness while hospitalized in an intensive care unit. The patients all died of other causes than digitalis intoxication. Cases 1, 2, 6 and 9 (Table 1) are subjects who died within 3 h after the last digoxin application. The glycoside blood levels

9-91

Table 1. Post mortem changes of digoxin blood levels of digitalised subjects

Blood specimens	Case 1	2	3	4	5	6	7	8	9	10
Before death	5.4	4.9	1.2	2.5	–	4.1	3.8	2.1	5.4	0.9
30 min after death	5.1	4.8	–	2.6	0.8	3.9	–	–	4.3	–
Femoral vein at autopsy	7.2	6.6	0.9	3.1	3.1	5.9	4.9	2.2	7.2	1.8
Heart at autopsy	8.1	11.1	1.5	2.8	2.9	15.1	7.7	5.4	–	3.1

before and after death were compared with femoral vein and with left ventricle heart blood specimens at autopsy. In some of the heart blood samples we observed an impressive post mortem rise of the cardiac glycoside concentrations up to 11–15 ng/ml (Table 1). The increase is up to 2.5 fold with a tendency to higher increases at higher vein blood levels. The femoral vein blood levels were only slightly increased at autopsy. Iisalo and Nuutila in 1973 reported some of these observations. Obviously a new equilibrium between the blood and tissues is established with time after death as already suggested by Doherty et al., 1967. The ratio of myocardial to serum concentrations is approximately 30 : 1. The breakdown of membrane functions with the time after cell death clearly explains such a post mortem rise by a diffusion *equilibrium*. While this may be plausible for heart blood there is no convincing explanation for vein blood. The concentration gradient between vein blood and muscle tissue is not very marked (Table 2). Skeletal muscles contain between 10 and 20 ng/g digoxin equivalents (Coltart et al., 1972; Haasis et al., 1977; Karjalainen et al., 1974). Cardiac glycosides are known to cause an elevation of arterial blood pressure in part by a direct action on peripheral vessels (Williams et al., 1958). Mason and Braunwald (1964) demonstrated increases of mean arterial pressure, systematic vascular resistance and vasomotor tone after intravenous injection of ouabain. These reactions indicate interactions between cardiac glycosides and receptors in the smooth muscle tissue contained in arteries and veins to a more or less extend. A binding of cardiac glycosides to tissue proteins and a post mortem release may be responsible for the observed concentrations differences. However the corresponding tissue concentrations are not so far investigated up till today.

The vein blood level in a case of suicide was 21 ng/ml digoxin equivalents. This level indicates a fatal poisoning but as shown by Bodem et al. (1977) a level of 20 ng/ml may still be survived after severe intoxications. We found digoxin blood levels in patients with terminal illness between 0.8 and 5.4 ng/ml. At autopsy one vein blood level was 7.0 ng/ml compared to 4.3 ng/ml shortly after death. All patients obtained therapeutic doses depending on the body weight (0.055 mg digoxin/kg bodyweight, daily i.v. application at 11 h a.m.). Thus a post mortem level of 7 ng/ml digoxin equivalents is not indicative for a fatal overdose as recently suggested by Phillips (1974). Plasma digoxin levels followed by radioimmunoassay after chronic administration of 0.72 and 0.36 mg digoxin to healthy subjects (Rietbrock and Abshagen, 1973). Peak levels of 3.3–6.8 ng/ml, were reached between 30 and 60 min after each administration. Levels of approximately 5 ng/ml even cannot give

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Table 2. Concentrations in ng/ml or ng/g wet weight of digoxin or digoxin equivalents in body fluids and tissues

	1	2	3	4	5	6	7	8
Blood	30,3	4,6 ± 2,3	29,6 (a) 12,0 (b) 2,6 (c)	150	–	–	< 7	22,3
Serum	–	–	–	–	2,3 ± 0,63	1,2 ± 8	–	–
Vitreous humor	–	–	–	–	–	–	< 5	10,5
Liquor	–	–	–	–	–	–	< 5	13,7
Brain	0,86	–	–	–	–	–	6,1 ± 2,5	9,7
Liver	35,5	68 ± 51	–	230	–	–	66 ± 50	81
Kidney	130,0	123 ± 65	–	680	–	–	140 ± 35	1400
Mycard l.	51,6	112 ± 67	200 (a) 282 (b) 158 (c)	200	105 ± 27,3	77,7 ± 43,3	80 ± 22	43 formalin treated
Myocard r.		97 ± 59			74 ± 14,0		71 ± 19	
Lung	–	–	–	–	–	–	16,2 ± 8,1	53
Skeletal muscle	–	20 ± 13	–	–	14,7 ± 10,4	11,3 ± 49	–	–

1 Selesky et al., 1977
2 Karajalainen et al., 1974 (after long terme therapy $n = 13$
3 Iisalo and Nuutila, 1973 (a, b after overdose, c therapeutic)
4 Steentoft, 1973 (fluorim. assay)
5 Haasis et al., 1977
6 Coltart et al., 1972
7 Own measurements (digitalised subjects $\eta = 5$)
8 Own measuremtnts (suicide)

evidence for a digoxin overdose even if lower concentrations in hemolised blood of approximately 12% are taken into account (Holt and Benstead, 1975). A history of digoxin toxicity is not thereby ruled out but without other contributions a death may not be explained by such levels. Thus it is important to know the time lag between the last administration and death. The time after which a maximum blood level of digoxin is reached after the ingestion of overdoses seems to be an additional difficulty. In patients being in intensive care the peak levels of 20 ng/ml and 10.2 ng/ml reported by Bodem et al. (1977) were reached after 12 and 15.5 h and after ingestion of 5 and 10 mg respectively. Other authors also recognized a delayed blood level maximum after digoxin overdoses (Citrin et al., 1972; Hobson and Zettner, 1973).

Because of a complicated concerted action between tissue concentrations, saturation of binding proteins and the concentration in the different body fluids at least the concentrations in kidney and heart tissue should be measured. While blood levels already fall, these tissue concentrations may still rise and thus give additional information. In a publication presented by T. E. Vorpahl and J. I. Coe (1978) during the evaluation of our findings similar observations of ante and post mortem digoxin blood levels were reported. These authors propose a combination of femoral venous serum and vitreous humor values to give the best information of an ante mortem digoxin toxicity.

9-93

Digoxin Measurements in Post Mortem Tissue Samples

Table 2 reviews some of the few, more or less complete data of tissue concentrations including those of fatal poisonings (Coltart et al., 1972; Haasis et al., 1977; Iisalo and Nuutila, 1973; Karjalainen et al., 1974; Selesky et al., 1976; Steentoft, 1973). Columns 7 and 8 show our measurements in five cases. The concentrations determined by us are compatible with the findings of others.

A highlighted point is the marked difference between renal tissue concentrations in normally digitalised patients and in the case of suicide. After ingestion of an unknown dose a ten fold increased kidney concentration was found. The accumulation of cardiac glycosides in renal tissue and heart may be due to the high content of sodium/potassium dependant ATP-ase, which is believed to be a specific receptor for these types of drugs (Dutta and Marks, 1972). The low glycoside content in the heart tissue of our suicidal case is due to formic aldehyde treatment in the heart tissue. In general however a comparison of RIA tissue measurements has to be made with caution.

Identification of Individual Cardiac Glycosides

There is few knowledge about the share and the pharmacokinetics of the corresponding metabolites which contribute to the values of the cardiac glycoside measurements. Most of the antisera used for radioimmunoassay do not distinguish between the parent compounds and their metabolites. In clinical practice is no need to separate these compounds because of comparable pharmacologic actions. The individual levels of the cardiac glycoside metabolites however may be of importance for the forensic toxicologist. Because of the possibility of a different metabolic fate at least informations of chronic or single doses might be obtained.

The metabolites all turned out to be 100% cross reactive in our radioimmunoassay if the steroid nucleous is not altered. Using a thinlayer chromatographic analysis by radioimmunoassay detection (Fig. 2) we analysed the ingested drug in the above mentioned suicidal case. In the vein blood we found methyldigoxin (Lanitop®) being extensively metabolised to digoxin. The digoxin peak shows a long tailing. It may additionally contain digoxin metabolites with digitoxide residues splitted off. The total amounts being in question are no more chemically detectable. This digoxin fraction has to be further investigated for a contribution of metabolites using an improved chromatographic separation method. During a 6 h period after administration of 0.5 mg digoxin only in the serum of one of two subjects the digoxigenin metabolite was detectable after 30—60 min in a concentration of 1.3—1.0 ng/ml. Digoxin was found in a concentration of 1.5—3.2 ng/ml during the same period (Loo et al., 1977). For this study the combination of high performance liquid chromatography and radioimmunoassay (HPLC-RIA) was applied.

Conclusion. Our study indicates that blood levels alone are no appropriate means to make a final decision in alleged cases of fatal poisonings. Radioimmunological blood level measurements only give evidence for a digitalised toxicity. There is a high difference in kidney concentrations between normally digitalized patients and a case

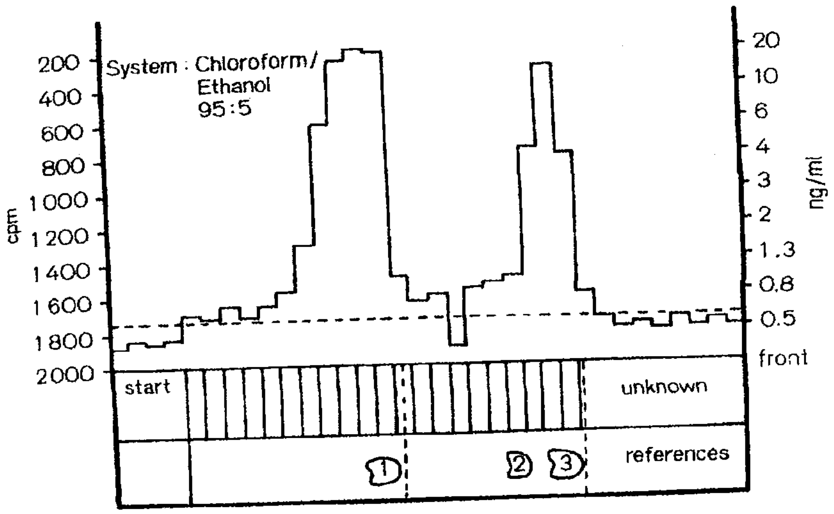

Fig. 2. Thin layer chromatographic analysis of cardiac glycosides by RIA detection. 5 ml of blood extracted, 0.5 mm zones removed from the layer, analysed after extraction. 1 = digoxin, 2 = or β-acetyldigoxin, 3 = methyldigoxin. Acetyldigoxin was not contained in the blood specimen

of suicide. Such differences were also found by Friedrich, G. (Institute of Forensic Medicine, Freiburg, GFR, personal communication, May 5, 1977). The renal tissue and the heart show the highest tissue concentrations. An interpretation of glycoside blood levels should be based on data taking the concentrations of heart and kidney into consideration. A chromatographic analysis by radioimmunoassay detection may give further information about the individual cardiac glycoside and its metabolism.

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9-96

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Fatal blood and tissue concentrations of more than 200 drugs

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Abstract

Fatal drug concentrations in body fluids and tissue samples are presented for more than 200 drugs and chemicals of toxicologic interest. Additionally, a reference list is added with more than 600 original papers concerning intoxications with a lethal outcome. The data can be helpful for the interpretation and plausibility control in own cases of intoxication. However, they should be used with caution, because use of drug data without sufficient knowledge about the patient or victim, the circumstances of the case, and about toxicokinetics and toxicodynamics might give a wrong interpretation in a special case.

Keywords: Drug concentrations; Intoxication; Fatalities; Forensic toxicology

1. Introduction

Approximately 400,000 inquiries per year are reaching German Poisoning Centers and more than 5000 persons die of an intoxication as the cause of death [363,534]. In postmortem toxicology the interpretation of drug data requires a good understanding of the pharmacology of the drugs in question. However, further details of the subject under question are necessary, i.e. age, general health, knowledge of the drug-taking history and the circumstances of the death. Also factors affecting postmortem blood concentrations of drugs have to be taken into account, such as chemical instability, action of endogenous enzymes, action of bacterial-derived enzymes, drug redistribution and other processes [148,505]. For the evaluation of quantitative chemical–toxicological findings in blood and serum samples a set of tables and data collections is available concerning therapeutic, toxic and comatose–lethal concentration ranges of usual medicaments and drugs [466,506,507,535,564,597]. Additionally Baselt and Cravey presented in a single, convenient source essential information on the disposition of chemicals and drugs most frequently encountered in cases of human poisoning [43]. Further pharmacokinetic and pharmacodynamic data are of interest such as plasma half-lives, distribution volumes, plasma protein binding, or pK_a values. Since these data were usually determined with living persons and organ-healthy people, they are however only limited value for the evaluation of findings raised in bodies. This applies also to the extrapolation of taken up quantities as well as the concentration at the time of the death. In summary, the proof of an intoxication as cause of death is usually made by the quantitative proof of a substance impairment in the appropriate concentration range and the exclusion of competitive causes of death with consideration of the circumstances of the death (Table 1).

The aim of the following data collection is to present a source of drug concentrations in different body fluids and tissue samples determined in cases of probably fatal intoxication found in the literature (see reference list). The data can be helpful for the interpretation and plausibility control in own cases. However, they should be used with caution, because use of drug data without sufficient knowledge about the patient or victim, the case, and about pharmacokinetics or toxicokinetics and pharmacodynamics might give a wrong interpretation in a special case.

2. Remarks and list of abbreviations

Beside determined concentrations of various drugs further information were integrated into the following table. This include the age and sex of patients as well as the ingestion route and dose, information about the analytical methods used, and information about the cause of death and

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9-97

Table 1 (*Continued*)

Age M/W	Height	Weight	Lay-days	Time of surv.	Ingestion route	D	BAC	Hb. [mg/l]	Fb. [mg/l]	P/M	Urine [mg/l]	Stomach contents	Bile [mg/l]	Liver [mg/kg]	Kidney [mg/kg]	Vitreous humour [mg/l]	Brain [mg/kg]	Muscle [mg/kg]	Analytical methode	Cause of death	Intoxication with:	Ref.
2moM	-	-	-	-	p.o.	-	-	0,51 unk.		-	-	-	0.6	-	-	0.1	-	-	GC/MS	OD	-	183
Diflunisal									*T1/2: 5-20 h*		*Vd: 0,1-0,2 l/kg*		*Therapeutic: 40-100 / 9-130*				*Toxic: 300-500 / -*					
38M	-	-	-	-	p.o.	-	-	260 unk.		-	78	34 mg	71	400	350	-	-	-	GLC	OD	B(th),N(th)	325
64W	-	-	-	-	p.o.	-	-	370 unk.		-	-	-	-	-	-	-	-	-	HPLC	OD	B(th)	572
W	-	-	-	-	p.o.	-	1.4	580 unk.		-	-	814 mg	-	-	-	-	-	-	HPLC	OD	At(th)	572
Digitoxin									*T1/2: 4-10 d*		*Vd: 41 l/kg*		*Therapeutic: 0,01-0,025 / -*				*Toxic: 0,03 / -*					
76W	-	-	-	-	p.o.	-	-	-	0.073	-	-	-	-	0.51	2.79	-	-	-	FPIA	OD	-	475
Digoxin									*T1/2: 30-45 h*		*Vd: 5,1-7,4 l/kg*		*Therapeutic: 0,0005-0,002 / 0,0007-0,022*				*Toxic: 0,0025-0,003 / 0,003-0,004*					
1mM	-	4,1kg	-	0,75h	i.v.	2mg	-	-	-	-	-	-	0.86	0.5	1.68	-	0.024	0.37	RIA	OD	-	217
20M	-	-	-	-	p.o.	-	-	0.01	-	-	-	0,8 mg/l	-	-	-	0.001	-	-	RIA	MDOD	Pr(le)	137
88W	-	-	-	-	p.o.	-	-	0.012		-	-	-	-	-	-	0.009	-	-	RIA	OD	-	137
18M	-	-	-	-	p.o.	-	0.2	-	0.019	-	0.58	1,1 mg/l	0.64	-	-	-	-	-	RIA	OD	-	282
82W	-	47 kg	-	1,5h	p.o.	5mg	-	0,02-0,025 Plasma		-	-	0,6 mg	-	0,1-0,11	0,13-0,15	-	-	-	RIA	OD	-	21
3dM	-	2,2kg	6h	~4h	i.v.	4mg	-	0,03 unk.		-	-	-	-	0.036	0.13	-	0.0009	-	RIA	OD	-	511
87W	-	-	-	-	p.o.	-	-	0.039	-	-	1.28	-	-	-	-	0.003	-	-	RIA	OD	-	137
64W	-	-	-	4 h	p.o.	-	-	0,05 unk.		-	-	-	-	-	-	-	-	-	RIA	OD	Ag(th)	403
3W	-	-	-	~3h	p.o.	-	-	0.077	0.071	-	-	-	-	0.22	0.52	-	-	0.16	FPIA	OD	-	201
50W	159 cm	53 kg	~7 d	1 h	p.o.	-	1.6	-	0.075	-	0.91	-	2.4	0.047	0.24	-	0.008	0.013	RIA	OD	-	472
78W	-	-	-	-	p.o.	-	-	-	0.098	-	-	-	-	0.73	1.5	0.048	-	-	FPIA	OD	-	474
40M	-	-	36h	-	p.o.	-	-	0,17 Plasma		-	7.8	2,4 mg	4.9	-	-	-	-	-	FPIA	MDOD	A(to)	150
2moW	-	4 kg	-	-	i.v.	-	-	0.2	-	-	-	-	-	0.2	-	-	-	-	RIA	OD	-	133
Dihydrocodeine			*Metabolite: Dihydrocodeine-6-glucoronide*						*T1/2: 3,4-4,5 h*		*Vd: 1,0-1,3 l/kg*		*Therapeutic: 0,03-0,25 / 0,03-0,25*				*Toxic: 0,5-1 / 0,5-2*					
30M	178 cm	66 kg	4 h	-	p.o.	-	-	2,6 (1,8)	1,9 (1,6)	1.3	-	-	-	1,3 (2,0)	10.6	-	0.8	-	HPLC	OD	B(th)	524
60M	-	-	-	-	p.o.	-	-	-	12	-	570	-	5340	620	-	-	-	-	GLC	OD	-	427
23M	-	-	-	-	i.v.	-	-	-	720	-	7	-	3	364	-	-	-	-	GLC	OD	Ba(tc)	427
Diltiazem					*Metabolite: Desacetyldiltiazem*				*T1/2: 5,1 h*		*Vd: 3-13 l/kg*		*Therapeutic: 0,03-0,13 / 0,05-0,4*				*Toxic: 0,8-1 / 3,7-6,1*					
21M	-	-	-	-	p.o.	1,5 g	1.4	1,5 unk.		-	-	-	-	-	-	-	-	-	-	OD	Hm(th)	495
68M	-	-	-	-	p.o.	-	0.8	2,5 unk.		-	-	5,4 g	-	-	-	-	-	-	-	OD	Pa(th),N(th)	495
W	-	-	-	-	p.o.	-	-	4 unk.		-	-	3,3 g	-	-	-	-	-	-	-	OD	-	495
66W	-	-	48h	-	p.o.	-	-	-	6.7	-	5.4	-	-	79	-	5.5	-	-	HPLC	OD	-	269
39M	-	-	-	-	p.o.	-	1.8	6.9	-	-	4.7	-	-	-	-	-	-	-	GC/FID	MDOD	Hm(th)	260
58M	-	-	-	-	p.o.	-	0.1	8 unk.		-	-	650 mg	-	-	-	-	-	-	-	OD	-	495
25W	-	-	-	4d	p.o.	-	1	8,49 Serum		-	4.48	-	-	-	-	-	-	-	GC/NPD	MDOD	Ae(to),Cc(to)	50
30M	175 cm	108 kg	-	-	p.o.	-	1.6	-	11	-	11	0,6 g	180	-	-	3.5	-	-	GC/FID	OD	-	229
61M	-	-	-	-	p.o.	-	1.2	15 (12) unk.		1.3	60 (10)	120 mg	-	41 (13)	-	-	-	-	GC/MS	OD	-	580
60M	-	-	-	20 h	p.o.	8 g	-	31 (9,7)		3.2	-	-	294.9	182 (47,3)	49,2 (22,6)	-	33.1	-	GC/MS	OD	-	493
58W	-	-	-	-	p.o.	-	-	33	-	-	-	1,8 g	-	-	-	-	-	-	GC/MS	OD	-	436
Diphenhydramine									*T1/2: 3-14 h*		*Vd: 3-4 l/kg*		*Therapeutic: 0,05-0,1 / 0,025-0,112*				*Toxic: 1-2 / 5*					
12wW	-	7,3 kg	-	-	p.o.	-	-	1,1 unk.		-	-	-	-	-	-	-	-	-	-	OD	-	36
12wM	-	7,2 kg	-	-	p.o.	-	-	1,1 unk.		-	-	-	-	5.5	3.6	-	-	-	-	OD	-	36
8wW	-	4,5 kg	-	-	p.o.	-	-	1.5	1.3	-	-	-	-	7.3	-	-	1.7	-	-	OD	-	36
6wW	-	3,6 kg	-	-	p.o.	-	-	1,6 unk.		-	-	-	-	-	-	-	-	-	-	OD	-	36
9wM	-	5,4 kg	-	-	p.o.	~60 mg	-	1,6 unk.		-	9	-	-	-	-	0.7	-	-	-	OD	-	36
28M	-	-	-	~14 h	p.o.	-	-	-	5	-	-	-	-	33.7	50.5	-	16	7.3	GC/NPD	OD	-	219
-	-	-	-	~12 h	p.o.	-	-	14.7	6.9	-	376	0,82 mg	-	-	-	-	-	-	GC/MS	OD	-	3
17M	-	-	-	-	p.o.	-	-	6,9 unk.		-	-	-	-	-	-	-	-	-	-	OD	-	514
25M	-	76 kg	-	-	p.o.	3 g	-	8,7 unk.		-	-	-	-	-	-	-	-	-	-	OD	-	514

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9-98

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State-Specific Mortality from Sudden Cardiac Death --- United States, 1999

Each year in the United States, 400,000--460,000 persons die of unexpected sudden cardiac death (SCD) in an emergency department (ED) or before reaching a hospital (*1*). Based on the latest U.S. mortality data, this report summarizes and analyzes 1999 national and state-specific SCD data. Reducing the proportion of out-of-hospital* SCDs would decrease the overall incidence of premature death in the United States. Heart attacks are the major cause of SCD; approximately 70% of SCDs are caused by coronary heart disease. National efforts are needed to increase public awareness of heart attack symptoms and signs and to reduce delay time to treatment.

National and state mortality statistics for this report were based on data from death certificates filed in state vital statistics offices and were compiled by CDC (*2*). Demographic data (e.g., age and race/ethnicity) listed on death certificates were reported by funeral directors usually from information provided by the family of the decedent. Causes of death on death certificates were reported by a physician, medical examiner, or coroner. Cardiac disease death was defined as one for which the underlying cause of death was classified and coded using the *International Classification of Diseases (ICD-10), Tenth Revision*, for diseases of the heart (codes I00-I09, I11, I13, and I20-I51) or congenital malformations of the heart (Q20-Q24[†]). SCD was defined for this report as a death from cardiac disease that occurred out-of-hospital or in an ED or one in which the decedent was reported to be "dead on arrival" at a hospital. Populations at risk were defined on the basis of U.S. census bureau estimates of resident populations; age-adjusted death rates were standardized by the direct method to the 2000 projected U.S. population (*3*).

Among 728,743 cardiac disease deaths that occurred during 1999, a total of 462,340 (63.4%) were SCDs; 120,244 (16.5%) occurred in an ED or were dead on arrival, and 341,780 (46.9%) occurred out-of-hospital. Women had a higher total number of cardiac deaths and higher proportion of out-of-hospital cardiac deaths than men (51.9% of 375,243 and 41.7% of 353,500, respectively), and men had a higher proportion of cardiac deaths that occurred in an ED or were dead on arrival (21.2% of 353,500 and 12.0% of 375,243, respectively) (Table 1). SCDs accounted for 10,460 (75.4%) of all 13,873 cardiac disease deaths in persons aged 35--44 years, and the proportion of cardiac deaths that occurred out-of-hospital increased with age, from 5.8% in persons aged 0--4 years to 61.0% in persons aged ≥85 years. SCDs accounted for 63.7% of all cardiac deaths among whites, 62.3% among blacks, 59.8% among American Indians/Alaska Natives, 55.8% among Asians/Pacific Islanders, and 54.2% among Hispanics. Whites had the highest proportion of cardiac deaths out-of-hospital, and blacks had the highest proportion of cardiac deaths in an ED or dead on arrival (Table 1).

The age-adjusted SCD rate was 47.0% higher among men than women (206.5 and 140.7 per 100,000 population, respectively). Blacks had the highest age-adjusted rates (253.6 in men and 175.3 in women) followed by whites (204.5 in men and 138.4 in women), American Indians/Alaska Natives (132.7 in men and 76.6 in women), and Asians/Pacific Islanders (111.5 in men and 66.5 in women). Non-Hispanics (217.8 in men and 147.3 in women) had higher age-adjusted SCD rates than Hispanics (118.5 in men and 147.3 in women).

In 1999, the state-specific proportion of all cardiac deaths that was SCD ranged from 57.2% (Hawaii) to 72.9% (Wisconsin) (Table 2). Other states with a high proportion of SCDs were Idaho (72.2%), Utah (72.1%),

Colorado (71.3%), Oregon (71.0%), Connecticut (70.5%), Rhode Island (70.0%), South Dakota (69.8%), Montana (69.6%), and Vermont (69.5%). Age-adjusted SCD rates (per 100,000 population) in 1999 ranged from 114.6 (Hawaii) to 212.2 (Mississippi).

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Editorial Note:

Despite advances in the prevention and treatment of heart disease and improvements in emergency transport, the proportion of cardiac deaths classified as "sudden" remains high, probably because of the unexpected nature of SCD and the failure to recognize early warning symptoms and signs of heart disease. The age-adjusted SCD rates and the state-specific variation in the proportion of SCDs suggest a need for increased public awareness of heart attack symptoms and signs. The finding that cardiac deaths out-of-hospital were more likely to occur among women than men is consistent with findings that women more often delay seeking help for heart attack symptoms (*4*). Early recognition of heart symptoms and signs leads to earlier artery opening treatment or defibrillation that results in less heart damage and deaths. Education and media efforts should inform the public about heart disease symptoms and signs, particularly women and young adults who might dismiss heart disease as a problem of men and the elderly (*5*). Health-care providers should be alert for atypical symptoms of heart disease among female and young adult patients (*6*).

The findings in this report are subject to at least three limitations. First, the cause of death information reported on the death certificate by the certifier is not always validated by a medical record or autopsy verification. The reliability and accuracy of the underlying cause of death also depend on the information reported by the certifier and on the state and national nosologists who determine the codes and the underlying causes. Second, because time of onset of disease symptoms and time of death are not available for analysis, the suddenness of death is determined arbitrarily and needs to be validated on the basis of clinical criteria on time frames. Third, data are subject to misclassification of race/ethnicity on death certificates, which might result in underestimating the number of deaths among American Indians/Alaska Natives, Asians/Pacific Islanders, and Hispanics and overestimating the number of deaths among blacks and whites (*7*).

The proportion of SCDs that occur out-of-hospital has increased since 1989 (*1*). Death and disability from a heart attack can be reduced if persons having a heart attack can immediately recognize its symptoms (*8*) and call 9-1-1 for emergency care. These symptoms are chest discomfort or pain; pain or discomfort in one or both arms or in the back, neck, jaw, or stomach; and shortness of breath. Other symptoms are breaking out in a cold sweat, nausea, and light headedness (*9*). Prevention of the first cardiac event through risk factor reduction (e.g., tobacco control, weight management, physical activity, and control of high blood pressure and cholesterol intake) should continue to be the focus of public health efforts to reduce the number of deaths from heart disease. Education and systems support to promote physician adherence to clinical practice guidelines and more timely access to emergency cardiac care also are important to the prevention and early treatment of a heart attack. Prehospital emergency medical service systems can assist in reducing SCD rates by dispatching appropriately trained and properly equipped response personnel as rapidly as possible in the event of cardiac emergencies. However, national efforts are needed to increase the proportion of the public that can recognize and respond to symptoms and can intervene when someone is having a heart attack, including calling 9-1-1, attempting cardiac resuscitation, and using automated external defibrillators until emergency personnel arrive.

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* A death that occurs in a nursing home, residence, and other unspecified place outside of a hospital.

† Diseases of the heart (ICD-10 codes I00-I09, I11, I13, and I20-I51) represent certain disease types (e.g., coronary heart disease, cardiomyopathy, dysrhythmias, and conduction system disorders, hypertensive heart disease, carditis and valvular heart disease, pulmonary heart disease, and heart failure). Congenital malformations of the heart (Q20-Q24) represent other disease types (e.g., congenital malformations of cardiac chambers and connections, cardiac septa, and pulmonary, tricuspid, and aortic and mitral valves). These codes are comparable to the ICD-9 codes of 390-398, 402, 404-429, and 745-746.

Table 1

TABLE 1. Number of cardiac deaths* and proportion of cardiac deaths, by location of death and selected characteristics — United States, 1999

		Location of death			
Characteristic	No.	In-hospital	Emergency department/ DOA†	Out-of-hospital	Data missing
Sex					
Men	353,500	36.6%	21.2%	41.7%	0.5%
Women	375,243	35.6%	12.0%	51.9%	0.5%
Age Group (yrs)					
0–4	2,508	77.4%	16.1%	5.8%	0.8%
5–14	436	47.0%	38.8%	13.1%	1.2%
15–24	1,291	33.7%	43.6%	21.8%	0.9%
25–34	3,311	28.0%	40.2%	31.0%	0.8%
35–44	13,873	23.8%	40.3%	35.1%	0.8%
45–54	35,216	26.2%	37.8%	35.4%	0.6%
55–64	64,322	33.8%	30.7%	34.9%	0.6%
65–74	129,414	41.2%	22.0%	36.3%	0.5%
75–84	226,326	41.3%	14.0%	44.2%	0.5%
≥85	251,999	31.1%	7.5%	61.0%	0.4%
Race/Ethnicity					
White	637,977	35.9%	15.4%	48.3%	0.4%
Black	79,153	36.9%	25.0%	37.3%	0.8%
American Indian/ Alaska Native	2,434	39.9%	18.5%	41.3%	0.3%
Asian/ Pacific Islander	9,179	43.7%	19.8%	36.0%	0.5%
Hispanic					
No	699,764	35.8%	16.4%	47.3%	0.5%
Yes	26,358	45.4%	18.1%	36.1%	0.4%
Total	**728,743**	**36.1%**	**16.5%**	**46.9%**	**0.5%**

* *International Classification of Disease, Tenth Revision*, codes I00-I09, I11, I13, I20-I51, and Q20-Q24.

† Death occurred in emergency department or dead on arrival to emergency department.

Return to top.

Table 2

TABLE 2. Number of all cardiac deaths, proportion of sudden cardiac deaths (SCDs), age-adjusted and age-specific rates*, by reporting area — United States, 1999

	All cardiac deaths	SCD			Age-specific SCD rates					
			Age-adjusted		0–34 yrs		35–64 yrs		≥65 yrs	
Area		%	No.	Rate†	No.	Rate	No.	Rate	No.	Rate
Alabama	13,489	62.9	8,481	194.1	113	5.3	1,821	108.3	6,547	1,152.7
Alaska	571	67.3	384	126.9	6	—§	142	58.0	236	679.1
Arizona	10,870	66.1	7,187	154.8	48	2.0	1,076	62.3	6,062	964.3
Arkansas	8,358	57.5	4,808	171.9	58	4.7	894	94.0	3,855	1,066.9
California	72,360	64.8	46,859	164.8	375	2.2	7,364	60.7	39,115	1,072.4
Colorado	6,476	71.3	4,615	140.1	61	3.1	809	48.6	3,745	918.4
Connecticut	9,169	70.5	6,463	170.0	37	2.4	864	67.3	5,562	1,187.0
Delaware	2,020	66.1	1,336	185.3	16	—	218	75.0	1,102	1,122.9
District of Columbia	1,661	65.7	1,091	191.3	10	—	223	105.7	857	1,188.6
Florida	51,608	60.5	31,243	155.0	208	3.1	4,381	77.1	26,648	971.9
Georgia	17,713	63.4	11,224	182.7	169	4.2	2,735	91.4	8,320	1,093.1
Hawaii	2,420	57.2	1,383	114.6	16	—	303	64.8	1,064	657.2
Idaho	2,558	72.2	1,847	160.3	17	—	277	60.1	1,553	1,093.4
Illinois	33,561	65.4	21,924	182.2	245	4.1	3,997	86.8	17,682	1,181.8
Indiana	16,750	61.3	10,272	175.3	106	3.6	1,759	77.5	8,407	1,131.5
Iowa	8,724	66.1	5,768	160.3	26	1.9	735	67.9	5,007	1,168.5
Kansas	7,013	61.8	4,335	146.9	24	1.8	591	59.7	3,720	1,050.6
Kentucky	12,162	58.4	7,103	184.1	73	3.8	1,405	90.4	5,624	1,140.4
Louisiana	12,080	59.3	7,162	183.2	99	4.4	1,703	104.6	5,360	1,068.9
Maine	3,436	66.5	2,286	165.3	11	—	318	62.3	1,957	1,116.0
Maryland	12,144	69.2	8,404	180.8	101	4.0	1,645	79.7	6,646	1,113.3
Massachusetts	15,907	65.8	10,462	150.7	83	2.8	1,449	60.5	8,930	1,038.7
Michigan	27,804	67.8	18,814	196.6	146	3.0	3,430	90.5	15,237	1,245.3
Minnesota	9,595	68.9	6,615	133.8	49	2.1	915	49.9	5,651	965.3
Mississippi	9,374	59.7	5,593	212.2	78	5.4	1,307	130.7	4,208	1,254.3
Missouri	18,052	65.5	11,819	198.9	89	3.4	1,904	91.5	9,826	1,317.7
Montana	2,055	69.6	1,430	149.9	4	—	215	60.0	1,211	1,032.9
Nebraska	4,517	66.6	3,009	156.9	25	3.0	374	60.6	2,610	1,143.3
Nevada	4,255	62.7	2,668	177.6	23	2.6	700	99.0	1,945	937.7
New Hampshire	2,759	68.0	1,875	164.3	11	—	300	63.0	1,564	1,081.7
New Jersey	23,581	57.6	13,571	156.8	93	2.5	1,906	58.6	11,571	1,044.1
New Mexico	3,486	68.1	2,374	156.2	20	2.3	389	59.2	1,964	982.1
New York	59,199	60.2	35,630	184.6	202	2.3	5,269	74.4	30,157	1,241.2
North Carolina	19,299	61.0	11,765	161.3	117	3.1	2,459	83.8	9,189	962.3
North Dakota	1,844	66.1	1,218	155.5	3	—	173	73.6	1,042	1,127.9
Ohio	33,338	64.5	21,514	185.3	156	2.9	3,525	81.7	17,832	1,187.9
Oklahoma	11,308	58.5	6,612	186.1	52	3.2	1,144	90.3	5,415	1,206.8
Oregon	7,306	71.0	5,189	146.8	43	2.7	815	61.9	4,331	995.4
Pennsylvania	41,838	66.1	27,644	189.5	154	2.8	3,986	85.8	23,502	1,237.6
Rhode Island	3,015	70.0	2,110	170.7	10	—	250	68.1	1850	1,198.6
South Carolina	10,028	62.3	6,247	175.5	92	4.8	1,546	102.8	4,609	973.7
South Dakota	2,031	69.8	1,418	161.7	6	—	200	75.3	1,212	1,149.4
Tennessee	16,358	60.2	9,844	184.6	106	4.0	2,120	97.9	7,618	1,118.7
Texas	43,717	59.5	26,006	162.1	295	2.8	5,192	69.8	20,517	1,017.5
Utah	2,830	72.1	2,039	139.1	30	2.3	284	44.2	1,725	929.4
Vermont	1,349	69.5	938	156.8	8	—	137	55.9	793	1,087.6
Virginia	15,401	59.3	9,130	152.4	106	3.1	1,813	66.8	7,210	930.5
Washington	11,590	67.0	7,763	145.1	55	1.9	1,130	49.9	6,578	1,000.7
West Virginia	6,860	59.0	4,045	193.7	29	3.6	799	110.2	3,217	1,178.8
Wisconsin	13,891	72.9	10,122	179.0	69	2.7	1,349	67.0	8,704	1,258.9
Wyoming	1,013	69.2	701	160.3	3	—	116	60.8	582	1,046.2
Average	728,743	63.4	462,340	175.4	3,976	3.0	78,456	75.4	379,869	1,099.8

* Per 100,000 population.
† Standardized to the 2000 projected U.S. population.
§ Number too small to calculate rate.

Return to top.

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Redistribution of diltiazem in the early postmortem period.

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Abstract

We determined tissue distribution of **diltiazem** after it was used to treat hypertension in two cases. The postmortem interval was 16 h in both cases. **Diltiazem** was isolated using liquid-liquid extraction, and it was identified and quantitated using gas chromatography-mass spectrometry (GC-MS) and GC, respectively. In one case, **diltiazem** concentrations in the lungs and pulmonary vessel blood were 62-82 and 27-30 times higher than right femoral blood, respectively. Although blood was not obtained from the left cardiac chambers, aortic blood showed a 10-times higher level of **diltiazem** than right femoral venous blood. **Diltiazem** concentration in blood in the right cardiac chambers was 3.6 times higher than that in right femoral venous blood. In another case, **diltiazem** concentrations in the lungs were 7.4-7.6 times higher than right femoral venous blood. Blood in the pulmonary arteries, pulmonary veins, left cardiac chambers, and aorta showed 2.0-3.1 times higher levels of **diltiazem** than right femoral venous blood. Blood in the right cardiac chambers displayed only 1.3 times higher level of **diltiazem** than right femoral venous blood. Our results strongly suggest that **diltiazem** accumulated in the lungs and was rapidly redistributed into pulmonary venous blood and then into the left cardiac chambers.

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9-105

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CASE REPORT

Fatal Unintentional Overdose of Diltiazem with Antemortem and Postmortem Values

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Background. Therapeutic errors involving calcium channel antagonists (CCA) resulting in death rarely have been reported in detail. We report a fatality from an unintentional overdose of sustained-release (SR) diltiazem including antemortem and postmortem blood concentrations. ***Case Report.*** A 65-year-old man with aortic stenosis mistakenly took six tablets of diltiazem 360 mg SR. He developed symptoms of toxicity by 7 hours after ingestion. By 10 hours, he went to the emergency department. Despite a prolonged resuscitative attempt, the patient died 17 hours postingestion. An antemortem blood sample drawn 11.5 hours after ingestion was 2.9 mcg/mL. Postmortem gas chromatography of central blood revealed a diltiazem level of 6 mcg/mL and the peripheral blood sample measured 5 mcg/mL. ***Conclusion.*** This case suggests that an unintentional overdose with a CCA may be lethal if the patient's cardiovascular ability to compensate for the toxic effects is compromised.

Keywords Fatal; Diltiazem; Antemortem; Postmortem

INTRODUCTION

Calcium channel antagonists (CCAs) are prescribed for the treatment of an extensive array of cardiovascular-related diagnoses and therapeutic errors may occur (1,2). We report a fatality from an unintentional overdose involving sustained-release diltiazem in a patient with aortic stenosis. Antemortem and postmortem blood levels were measured.

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CASE REPORT

A 65-year-old man with aortic stenosis mistook his diltiazem 360 mg sustained release tablets for his predental procedure antibiotic and ingested six tablets (2160 mg). Approximately 7 hours later, he had shortness of breath, dizziness, and diaphoresis. The patient's condition worsened over the next 3 hours and he was too weak to rise from a lying position. Upon arrival at the emergency department, the patient was diaphoretic, pale, and cyanotic. His blood pressure was 106/50 mm/Hg with a heart rate of 70 beats/min. The cardiac rhythm on a 12-lead electrocardiogram was interpreted as ventricular ectopy or atrial flutter with a possible 2:1 heart block. The patient was given a single oral dose of activated charcoal, 2 grams of intravenous calcium chloride, and supplemental oxygen, and was admitted to the intensive care unit approximately 3 hours after his arrival to the emergency department.

Approximately 30 minutes after arrival to the intensive care unit, the patient became unresponsive and developed cardiac arrest. Therapy consisted of calcium, dopamine, norepinephrine, glucagon, lidocaine, and external pacing. Cardiopulmonary resuscitation was also initiated. After a 3-hour resuscitative attempt, the patient was pronounced dead (17 hours after the ingestion).

Postmortem examination of the patient confirmed severe calcified stenosis of the aortic valve with associated left ventricular hypertrophy and cardiomegaly (780 grams). His heart had bilateral atrial dilatation and right ventricular dilatation. Other findings included agenesis of his left kidney with compensatory hypertrophy of his right kidney. There were multiple rib fractures and associated soft tissue hemorrhage that were deemed consistent with resuscitative efforts. No pill fragments were found in the gastric contents.

9-106

An antemortem blood sample drawn approximately 11.5 hours after ingestion was analyzed by gas chromatography and revealed a diltiazem concentration of 2.9 mcg/mL. Postmortem analysis by gas chromatography of the central blood revealed a diltiazem concentration of 6 mcg/mL and peripheral blood sample measured 5 mcg/mL. Deacetyldiltiazem and nordiltiazem were not measured.

DISCUSSION

CCAs exert their activity by inhibiting the influx of calcium into L-type calcium channels located primarily in cardiac and smooth muscle cells. This results in peripheral vasodilation, sinus node depression, impaired atrioventricular conduction, and negative ionotropic effects on the myocardium (3). In the overdose setting, resulting effects are hypotension, bradycardia, dysrhythmias, and circulatory collapse.

The diltiazem concentrations measured in our patient greatly exceed the reported therapeutic range of 0.04–0.2 mcg/mL for peripheral blood (4). The elevated diltiazem concentrations measured in our patient were consistent with the history of an excessive dose; however, the postmortem levels are lower than previously reported ranges associated with fatalities from diltiazem poisoning (5). The near doubling of blood concentrations from 11.5 hours antemortem to 17 hours postmortem might be a reflection of slower absorption due to the sustained-release formulation or the influence of saturated hepatic enzymes (3). Previous heart/femoral concentration ratios have averaged 2.6 with a range of 1 to 7 (6). Our patient had a ratio of approximately 1:2.

The postmortem examination also confirmed the presence of aortic stenosis and the cardiac pathology associated with it. This comorbidity may have contributed to the unstable hemodynamic status and compromised the resuscitative efforts. The vasodilatory effect of the toxic level of diltiazem in addition to its negative inotropic and chronotropic effects may have been a catastrophic combination for this patient, as his aortic stenosis limited his cardiovascular response to reduced systemic vascular resistance and diminished stroke volume.

In conclusion, an unintentional overdose of diltiazem resulted in the death of a patient with aortic stenosis. The antemortem blood concentration of diltiazem was 2.9 mcg/mL at 11.5 hours postingestion and the postmortem blood concentrations (at 17 hours postingestion) were 6 mcg/mL from a central site and 5 mcg/mL from a peripheral site.

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9-107

SHORT COMMUNICATION

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Retrospective Review of Digoxin Exposures to a Poison Control System following Recall of Digitek® Tablets

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Abstract

Background: In April 2008, Digitek® digoxin tablets were recalled by the manufacturer as possibly containing double the labeled amount of drug. The recall to March 2006 involved 800 million tablets.
Objective: The aim of this study was to evaluate whether there was any increase in the number of calls to a poison control system, and any increase in the severity of exposures after the recall compared with before the recall.
Methods: A retrospective review of all digoxin exposures to a poison control system from March 2004 to February 2008 was conducted, with data extracted from an electronic database (California Poison Control System). Total numbers of exposures were identified. Cases with moderate, major, and death outcomes were also identified and tallied. Chi-squared analysis was performed.
Results: Prior to the recall, there were 679 digoxin exposures. 148 (22%) were listed with moderate, major, or death as outcome. After the recall, there were a total of 610 cases, 165 (27%) with moderate, severe, or death as outcome. There was a statistically significant increase in the total number of moderate, major, and death outcomes after the period of the manufacturing error compared with before ($p = 0.028$).
Conclusion: During the period of manufacturing error, there was a statistically significant increase in digoxin exposures with moderate, major, or death outcomes. The recall of Digitek® tablets may have increased moderate, major, or death outcomes from digoxin exposures in a poison control system database.

Introduction

Digoxin is a cardiac glycoside used in the treatment of congestive heart failure and atrial fibrillation. It has a narrow therapeutic index, i.e. toxicity may be seen just above therapeutic concentrations. Digoxin poisoning is associated with a high incidence of morbidity and mortality.[1]

In April 2008, one manufacturer of digoxin tablets (Actavis Group) issued a voluntary Class I recall of its Digitek® brand digoxin tablets due to concern about a possible excessive drug concentration versus the labeled concentration.[2,3] A Class I recall is defined as "a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death."[4] The company reported "the possibility" that it had distributed double-strength tablets and recalled the entire unexpired production of its Little Falls, NJ, USA, plant, dating back to March 2006, a total of 800 million tablets.[5] The US FDA was aware of this recall.[4]

The Institute for Safe Medication Practices (ISMP) is a nonprofit multidisciplinary healthcare agency. The Acute Care edition of the ISMP newsletter is published bimonthly and intended to help all healthcare providers, consumers, and the pharmaceutical industry to prevent medication errors. ISMP Quarter Watch (second quarter 2008) reported that Digitek® accounted for more than 650 deaths as a result of a manufacturing error.[5]

The aim of our study was to review cases reported to a poison control system to evaluate whether there was an increase in the number of calls and in the severity of exposures to digoxin

9-108

from previous years before the recall compared with after the recall. Inquiries from telephone-based poison center networks are often the initial source of epidemiologic and demographic information about a harmful or hazardous substance, and all clinical case details are logged into an electronic database. Our null hypothesis was that no increase in the number of moderate, major, or death outcomes occurred during the period of the potentially excessively potent digoxin.

Methods

We performed a retrospective review of the electronic database (Visual Dotlab®) of the California Poison Control System (CPCS) from March 2004 to February 2008. We compared two time intervals: March 2004 through February 2006 (before manufacturing error) to March 2006 through February 2008 (after manufacturing error) using the search terms 'digoxin', 'Digitek®', and 'Lanoxin®'. The CPCS is the poison system for both health professionals and consumers, for the entire state of California, providing information and management advice. Callers access the CPCS by a toll-free number. Reporting to the CPCS is not mandatory.

Inclusion criteria were patients of any age or sex with an exposure to digoxin reported to the CPCS over the study period. Cases with incomplete records (e.g. patients lost to follow-up, unknown disposition or unknown outcome) were excluded. The total numbers of exposures were tallied. In addition, the total number of moderate, major, and death outcomes were identified. All data abstracted were keyed into Microsoft Excel 2003 (Redmond, WA, USA). A Z-test for two proportions was performed on the results.

This study was approved by the institution's Human Research Protection Program.

Results

During the period from March 2004 through February 2006 our database recorded a total of 679 digoxin exposures. Of these exposures, 148 (22%) cases had an outcome determined to be moderate, severe, or death. All cases except one moderate exposure were managed at a health-care facility, and there were 113 (17%) moderate and 29 (4%) major cases, with five (0.7%) deaths reported.

During the period from March 2006 through February 2008 there was a total of 610 exposure calls. All of these cases were managed at a health-care facility. Of these exposures, 165 (27%) had an outcome determined to be moderate, severe, or death. There were 137 (23%) moderate and 26 (4%) major cases. The incidence of death decreased to 2 (0.3%) during this period.

There was a statistically significant increase in the total number of combined moderate, major, and death outcomes during the potential manufacturing error period compared with before (two-tailed $Z=2.13$; $p=0.033$). The increase in proportion of symptomatic exposures found in our data was due to those with moderate outcomes.

Discussion

Digoxin is a cardiac glycoside used in the treatment of congestive heart failure and atrial fibrillation. Although controversial, digoxin has been suggested to decrease both morbidity and mortality in patients with congestive heart failure receiving therapeutic dosages.[6,7] However, both acute and chronic digoxin poisoning from elevated concentrations can be fatal.[1] Whilst there is a digoxin-specific immunoglobulin antidote, which has greatly reduced mortality,[8] the diagnosis of digoxin poisoning can often be overlooked. This is more common with chronic digoxin poisoning due to subtle non-cardiac signs and symptoms, such as nausea, abdominal pain, confusion, headaches, and visual changes.[1]

Adverse drug reactions have been associated with a high incidence of morbidity and mortality.[9] When associated with manufacturing errors, these effects can be devastating.[10,11] In the current study, there were some changes in the pattern of digoxin exposures reported to the CPCS before and after a potential 2-fold packaging error by a leading manufacturer. Although total cases decreased, there was a higher proportion of those with clinically significant outcomes. The increase in outcomes was primarily due to an increase in 'moderate' outcomes, while deaths actually decreased.

The major limitation of our study is in the retrospective use of poison center data. The certified specialists in the poison information staff of the CPCS use a standardized data collection form and outcome criteria.[12] However, there could be omissions from these records, and also this data may not accurately reflect true events. Another limitation is that there is no record of which actual digoxin product (erroneously vs correctly formulated) was available in each case. Furthermore, the exact time at which digoxin tablets were available to consumers may not exactly coincide with product availability and recall dates. In addition, clinicians might have called the CPCS for symptomatic patients, opting not to call regarding asymptomatic or minimally symptomatic patients, resulting in underreporting. Finally, clinicians knowing of the recall may have

9-109

called more frequently, although we attempted to control for this by only including cases reported before the recall announcement was made.

Conclusion

There was an increase in clinically significant symptomatic outcomes with the availability of erroneously packaged digoxin as reported to our poison control system. However, the number of digoxin-related deaths actually decreased during the period of the manufacturing error. A further confirmatory study would require nationwide analysis of data.

Acknowledgments

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9-110

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Correlation of Antemortem and Postmortem Digoxin Levels

The dynamics of digoxin metabolism have been well studied since the introduction of sensitive radioimmunoassay procedures capable of detecting low biologic levels of this compound [1]. The value of monitoring digoxin therapy through serum levels has been widely accepted, and toxic effects are frequently observed when the serum level of adult individuals exceeds 2 ng/ml [2,3]. Beller et al [4] reported a twofold increase in mortality among hospitalized patients having digitalis toxicity.

Only a few authors have reported on postmortem digoxin levels. Several of these have assumed that serum levels obtained from intracavitary myocardial autopsy specimens accurately reflect antemortem levels at the time of death [5-7]. Others have noted possible difficulties in interpreting postmortem values. Iisalo and Nuutila [8] in 1973 pointed out discrepancies between antemortem and postmortem serum digoxin levels in three cases and attributed this to "accumulated absorption," presumably prior to death. Karjalainen et al [9] in 1974 stated "the postmortem concentrations of blood digoxin are higher than those measured during life" but gave no explanatory or supporting data. Selesky et al [10] also thought that some of the elevated postmortem digoxin values seen in their series may have been due to the interval between death and sampling, although in the one case in which an antemortem specimen was analyzed there was no difference in value between the serum obtained before death and that taken at autopsy.

Holt and Benstead [11] in 1975 reported another problem with the interpretation of postmortem digoxin values. They demonstrated that digoxin levels on serum taken from heart blood at autopsy were consistently higher than levels on samples from the femoral veins, with the difference as great as 137% in their series. Dickson and Blazey [12] in 1977 stated they found a similar heart to venous blood ratio in one case and pointed out that most previous reports had not indicated the site from which the serum samples were obtained.

The purpose of the present study is fourfold: to determine the discrepancies that exist between antemortem and postmortem digoxin levels, to learn if such differences can be related to the postmortem interval, to substantiate variation in postmortem blood values between samples taken from different sites, and finally to establish the most accurate way of estimating digoxin toxicity from postmortem specimens.

Materials and Methods

Twenty-seven autopsy cases from two county hospitals were studied. Postmortem samples from the left ventricular cavitary blood and vitreous humor were obtained in all cases. Sub-

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9-111

clavian and femoral venous blood samples were obtained in 24 and 11 cases, respectively. All patients were receiving therapeutic doses of digoxin by various routes of administration for at least one week prior to death. No cases of suicidal or acute accidental poisoning were included. Antemortem serum samples were available for analysis in all cases, and the last digoxin dose was administered a minimum of 4 h before an antemortem sample was obtained. The blood urea nitrogen and interval between death and postmortem sampling (postmortem interval) were recorded.

Samples were centrifuged immediately, and the serum was refrigerated at 4°C. Assays were performed within 72 h. In one hospital (St. Paul-Ramsey) assays were performed with material from Corning Medical Diagnostics, while in the second institution (HCMC) the materials used were from New England Nuclear. The procedure in either case was based on the principles of Smith et al [1] and involved the competitive binding of ^{125}I-labeled digoxin and unlabeled digoxin (present in the serum or vitreous sample) with a specific rabbit anti-digoxin antibody. The digoxin bound to antibody was separated by absorbing out the unbound digoxin (both labeled and unlabeled) with charcoal. In the Corning procedure this step was omitted because the antibody was precoated to glass beads. The bound fraction was counted with a gamma scintillation counter, and the percentage of bound ^{125}I-labeled digoxin was calculated. The digoxin level in the sample was determined from a standard curve, constructed daily by using five standards. Corning and New England Nuclear standards ranged from 0 to 5.0 ng/ml and 0.5 to 8 ng/ml, respectively. There was no difficulty in performing the postmortem tests with either procedure. The results were both internally consistent and showed good correlation between the two institutions when analyzed statistically.

The time from antemortem sampling to death ranged from 1 to 48 h, with a mean of 7.7 h. It was therefore necessary to correct for continued metabolism of the drug during the interval between the antemortem sample and death by determining the drug half-life in each case. Approximately 90% of digoxin was excreted unchanged by the kidney, and the half-life was therefore related to renal function. Each patient had a blood urea nitrogen (BUN) test performed within one day of death, and drug half-lives were determined by using data published by Jelliffe [13]. The immediate antemortem digoxin level was then calculated by using the formula

$$\ln N_t = \ln N_0 - \ln 2(t/T\tfrac{1}{2})$$

where

N_t = serum digoxin level at time of death,
N_0 = serum digoxin level at time of antemortem sampling,
t = time interval between drawing of antemortem sample and death, and
$T\tfrac{1}{2}$ = digoxin half-life based on BUN [13].

Results

Postmortem intervals ranged from 1.0 to 22.4 h, with a mean of 10.8 h. Compared to antemortem levels, average postmortem serum digoxin levels were significantly higher ($P < 0.001$) in samples taken from the heart, subclavian vein, and femoral vein (Table 1). Postmortem cardiac serum levels exceeded antemortem levels in all 26 cases where the postmortem interval was greater than an hour, and in no case did the postmortem level fall below the antemortem values on samples from heart or subclavian vein. In contrast, 2 of the 11 cases in which femoral samples were drawn had lower postmortem serum values than the corresponding antemortem levels (Cases 1 and 26). The mean of postmortem to antemortem ratios was 1.96 for heart, 1.63 for subclavian, and 1.42 for femoral samples. Vitreous levels were somewhat more variable, with 23 falling below, 3 exceeding, and 1 equaling antemortem levels. The mean ratio of vitreous to antemortem values was 0.71.

2-3

9-112

No useful correlation could be made between postmortem interval and either the absolute or relative change in postmortem samples, regardless of the site of sampling (Table 2). Case 9 had the shortest postmortem interval and the least amount of change; however, this trend did not hold true for a major portion of the cases. Case 17 showed the greatest relative increase in heart level with a postmortem interval in the mid-range, while Case 2, with a much longer postmortem interval, showed the second lowest change of the series.

If a diagnosis of digoxin toxicity were to be made on the basis of serum levels equal to or greater than 2 ng/ml, 48% of patients in this series would have been so diagnosed with the immediate antemortem value. With the postmortem heart samples, the figure would rise to 89%. Similarly, subclavian and femoral samples also lack specificity for digoxin toxicity. However, a postmortem serum level below 2 ng/ml does appear to be strong evidence against toxic levels in the antemortem stage.

Although the vitreous concentrations also differed markedly from true antemortem concentrations, they were more accurate indicators of toxicity. Ten patients (37%) had vitreous levels equaling or exceeding 2.0 ng/ml. Each of these ten cases also had a toxic antemortem serum level. Only three cases of possible toxicity (based on elevated antemortem levels) were not detected by vitreous determinations.

TABLE 2—*Ratio of postmortem to antemortem digoxin levels and relationship to postmortem interval (PMI).*

Case	PMI, h	Postmortem to Antemortem Ratio: Heart	Subclavian	Femoral	Vitreous
1	17.0	1.63	1.15	0.96	0.67
2	15.2	1.22	1.15	...	0.30
3	5.7	1.33	1.27	...	0.64
4	19.0	1.96	2.04	1.56	0.79
5	13.0	1.95	1.88	1.40	0.95
6	21.0	1.84	2.08	...	0.55
7	20.9	1.68	1.65	...	0.62
8	4.0	1.31	1.18	...	0.47
9	1.0	1.00	1.11	...	0.52
10	13.5	2.17	1.83	1.29	0.83
11	10.8	2.04	1.91	1.59	0.95
12	16.3	2.70	1.60	...	1.20
13	6.5	1.75	...	...	0.75
14	16.2	2.47	1.63	1.52	0.74
15	14.0	2.78	...	...	1.00
16	22.4	1.38	1.25	...	0.38
17	11.3	3.00	...	...	0.81
18	4.4	1.25	1.12	...	0.69
19	15.0	2.50	1.86	...	0.36
20	10.8	2.28	1.50	...	0.43
21	3.5	1.78	1.57	1.43	0.50
22	2.5	1.31	1.00	...	0.54
23	3.8	1.92	1.33	1.08	0.33
24	3.4	2.24	1.42	1.83	0.83
25	3.0	2.90	2.50	2.30	1.10
26	16.0	2.00	1.50	0.67	0.67
27	6.8	2.67	3.00	...	1.67
Mean	10.6 ± 6.26	1.96 ± 0.56	1.63 ± 0.48	1.42 ± 0.44	0.71 ± 0.30
Correlation with PMI, *r*	...	0.15	0.14	0.48	−0.06

2-5

9-113

TABLE 1—*Comparison of antemortem and postmortem serum digoxin levels.*

Case	BUN,[a] mg/dl	Serum Digoxin Levels, ng/ml[b]					
		Antemortem		Postmortem			
		At Time of Sampling	Calculated for Time of Death	Heart	Subclavian	Femoral	Vitreous
1	24	17.3	15.8	25.8	18.2	15.2	10.4
2	27	8.2	8.0	9.8	9.2	...	2.4
3	122	6.6	6.6	8.8	8.4	...	4.2
4	59	5.1	4.8	9.4	9.8	7.5	3.8
5	44	4.5	4.0	7.8	7.5	5.6	3.8
6	70	4.0	3.8	7.0	7.9	...	2.1
7	100	3.5	3.4	5.7	5.6	...	2.1
8	87	3.3	3.2	4.2	3.8	...	1.5
9	94	2.7	2.7	2.7	3.0	...	1.4
10	41	3.0	2.4	5.2	4.4	3.1	2.0
11	14	2.7	2.2	4.5	4.2	3.5	2.1
12	150	2.1	2.0	5.4	3.2	...	2.4
13	30	2.3	2.0	3.5	...	...	1.5
14	20	2.0	1.9	4.7	3.1	2.9	1.4
15	22	1.8	1.8	5.0	...	...	1.8
16	78	1.9	1.6	2.2	2.0	...	0.6
17	28	1.9	1.6	4.8	...	...	1.3
18	75	1.7	1.6	2.0	1.8	...	1.1
19	56	1.6	1.4	3.5	2.6	...	0.5
20	90	1.5	1.4	3.2	2.1	...	0.6
21	16	1.5	1.4	2.5	2.2	2.0	0.7
22	40	1.4	1.3	1.7	1.3	...	0.7
23	14	1.2	1.2	2.3	1.6	1.3	0.4
24	22	1.4	1.2	2.7	2.3	2.2	1.0
25	56	1.8	1.0	2.9	2.5	2.3	1.1
26	22	0.6	0.6	1.2	0.9	0.4	0.4
27	20	0.5	0.3	0.8	0.9	...	0.5

[a] All urea nitrogen values were obtained from blood specimens drawn less than 24 h before death.
[b] All cases in which a femoral specimen was obtained were from one institution (HCMC) and the materials for assay were supplied by New England Nuclear. The remaining tests were performed in the second hospital with assay material from Corning Medical Diagnostics.

2-4

9-114

Discussion

It is clear from this investigation that postmortem digoxin levels taken from cardiac blood, venous blood, or vitreous humor do not mirror the antemortem levels. Substantial increases in serum levels occur following death, irrespective of the source of the sample. It seems probable that a new drug equilibrium between blood and tissue is established after death. Several investigators have found various tissue levels to exceed blood levels, with the highest concentrations occurring in the heart and kidney [*8,9,14*]. The ratio of myocardial to serum concentrations is approximately 30:1. With cell death and subsequent loss of membrane integrity, digoxin must diffuse from tissue into the adjacent circulatory compartment. As a consequence it is possible to falsely diagnose digoxin toxicity from postmortem serum specimens no matter what the source of the samples, but a postmortem serum level below 2 ng/ml will exclude the presence of toxic levels in the antemortem state.

Conversely, vitreous levels are usually below the true antemortem values. The vitreous compartment appears to be less permeable to compounds in the circulation. DiMaio et al [*6*] have suggested that vitreous to serum ratios less than one reflect rising blood levels at the time of death and those greater than one reflect falling levels. Our data do not support such a concept. All patients died between 6 and 120 h after their last dose. Since the time required for equilibration with blood and myocardium is usually less than 4 h after oral administration, blood levels should have been falling in every case. It is possible that in most individuals vitreous levels never equilibrate with blood. However, this series does establish that significantly elevated vitreous levels correspond with toxic antemortem serum levels.

A larger series correlating true antemortem with postmortem concentrations might establish a serum or vitreous threshold concentration that most accurately reflects the clinical situation. In the absence of such a threshold concentration for guidance, we think that a combination of venous serum and vitreous humor values provide the most useful information. Femoral samples appear preferable to subclavian.

A striking finding of this study is that 14 of 27, or 52%, of the patients had toxic levels at the time the antemortem samples were drawn, most of which were obtained for electrolyte or cardiac enzyme determination. Digoxin toxicity was thought to be the cause of death in Case 1 and may well have been a contributory factor in the deaths of Cases 2, 3, and 4. We have found this type of retrospective analysis useful and strongly recommend saving serum for five to seven days in the laboratory. The cardiac glycoside dosage is frequently not adjusted for acute renal failure or renal hypoperfusion commonly seen in severely ill patients.

This investigation also raises suspicion regarding many studies in postmortem toxicology. If indeed a new blood-tissue equilibrium is established with digoxin after death, a similar situation may exist for many compounds studied during autopsy. Gee [*15*] has already reported varying barbiturate levels between cardiac and femoral vein specimens, with differences as high as 6.0 mg/100 ml. Other drugs whose postmortem distribution through the vascular system is more uniform than barbiturate might show significant variations between specimens drawn during life and after death.

Summary

Postmortem serum digoxin levels from any source routinely exceed antemortem values. Variation resulting from site of sampling gave a mean postmortem to antemortem ratio of 1.96 for heart, 1.63 for subclavian vein, and 1.42 for femoral vein samples.

No correlation could be made between the postmortem interval and the increase in postmortem serum values, irrespective of the site of sampling.

A combination of femoral venous serum and vitreous humor values gave the best information for determining possible antemortem digoxin toxicity.

2-6

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2-7

9-116

ORIGINAL ARTICLE ARCHIVE

Digitalis Intoxication — A Prospective Clinical Study with Serum Level Correlations

George A. Beller, M.D., Thomas W. Smith, M.D., Walter H. Abelmann, M.D., Edgar Haber, M.D., and William B. Hood, Jr., M.D.

N Engl J Med 1971; 284:989-997 | May 6, 1971

Abstract

A prospective study of 931 consecutive patients admitted to a medical service was undertaken to describe the prevalence and epidemiology of cardiac digitalis toxicity, and to correlate serum concentrations of digoxin and digitoxin by radioimmunoassay with clinical and biochemical data. Fifteen per cent of the patients surveyed were taking digitalis on admission, and of these, 23 per cent were definitely and 6 per cent possibly digitalis toxic by serial electrocardiograms. There was a significantly greater prevalence of advanced heart disease, underlying atrial fibrillation, anorexia, acute or chronic pulmonary disease and renal failure in toxic than in nontoxic patients. Mortality was more than twice as high in the toxic group. Serum drug concentrations were significantly higher in toxic than in nontoxic patients. This study of patients entering a large city hospital demonstrated a high prevalence of digitalis intoxication, which had an ominous prognosis.

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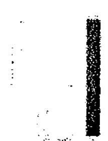
MEDIA IN THIS ARTICLE

FIGURE 1



Mortality in 922 Definitely Toxic, Nontoxic and Other Remaining Patients Hospitalized during the Period of Study (the Nine Possibly Toxic Patients Are Omitted).

FIGURE 2

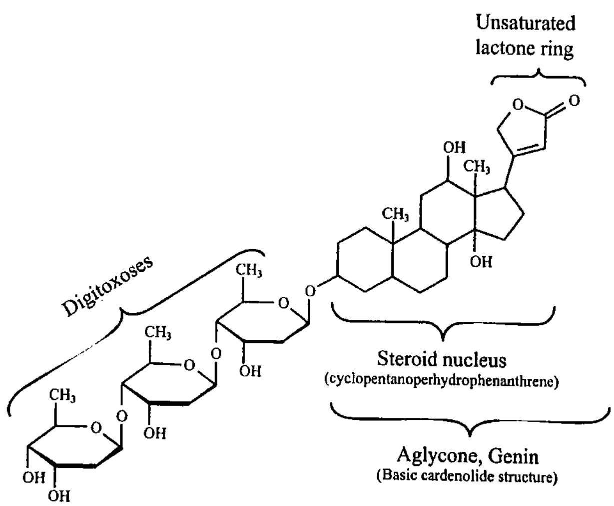
Serum Digoxin and Digitoxin Concentrations Determined by Radioimmunoassay in Nontoxic (Stippled Bars) and Definitely Toxic (Crosshatched Bars) Patients, Presented as Mean ± S.D. (Numbers of Patients in Each Group Are Shown in Parentheses).

9-117

CHAPTER 62

Cardioactive Steroids

Jason B. Hack • Neal A. Lewin



Digoxin
MW: = 780 daltons

A 92-year-old woman was brought to the hospital by her grandson. The grandson stated that she had lost her appetite for several days, refused her medications for 2 days, and had begun to vomit on the day of admission. The woman complained of being weak and having no appetite because of her constant nausea. Her past medical history was significant for congestive heart failure and hypertension, for which she was chronically treated with digoxin, furosemide, and enteric-coated aspirin. Her grandson reported that 4 days prior to admission, she had initiated a course of clarithromycin for sinusitis.

On presentation to the emergency department (ED), the patient was not in acute distress, and was alert and oriented to place and person but not to time. Her vital signs were: blood pressure, 140/95 mm Hg; pulse, 50 beats/min and regular; respiratory rate, 16 breaths/min; and rectal temperature, 98.8°F (37.1°C). The woman weighed 121 lbs (55 kg). Her neck was supple with no jugular venous distension or carotid bruits appreciated. Auscultation of the lungs revealed bibasilar crackles. Cardiac auscultation revealed a normal S_1, S_2, and an S_3 gallop, with no audible murmurs. Abdominal examination revealed a soft abdomen with increased bowel sounds and without masses or bruit. Examination of the patient's lower extremities revealed 1+ pitting edema without clubbing or cyanosis, and all pulses were 2+. Neurologic examination was nonfocal.

The patient was attached to a cardiac monitor with continuous pulse oximetry. An IV line was inserted, and blood samples were obtained for complete blood count (CBC); electrolytes, including calcium and magnesium; blood urea nitrogen (BUN); creatinine; glucose; liver enzymes; lipase; digoxin; and salicylate levels. The electrocardiogram (ECG) revealed high-degree heart block with a ventricular rate of 30–50 beats/min (Fig. 62–1), which then converted spontaneously to atrial flutter with variable block and a ventricular response rate of 30–40 beats/min (Fig. 62–2). Transcutaneous pacer pads were placed on the patient in standby mode, while 5 vials of digoxin-specific Fab were requested. Stat laboratory results revealed serum sodium, 142 mEq/L; chloride, 114 mEq/L; potassium, 3.6 mEq/L; bicarbonate, 24 mEq/L; BUN, 12 mg/dL; creatinine, 1.4 mg/dL; glucose, 98 mg/dL; calcium, 9.8 mg/dL; magnesium, 2.0 mEq/L. Liver enzymes, lipase, and CBC were all normal. A serum digoxin concentration was pending.

Fifteen minutes after the examination was completed, the patient vomited. Although her heart rate decreased to 30 beats/min, her blood pressure remained at 130/80 mm Hg. Atropine 1 mg IV was

9-118

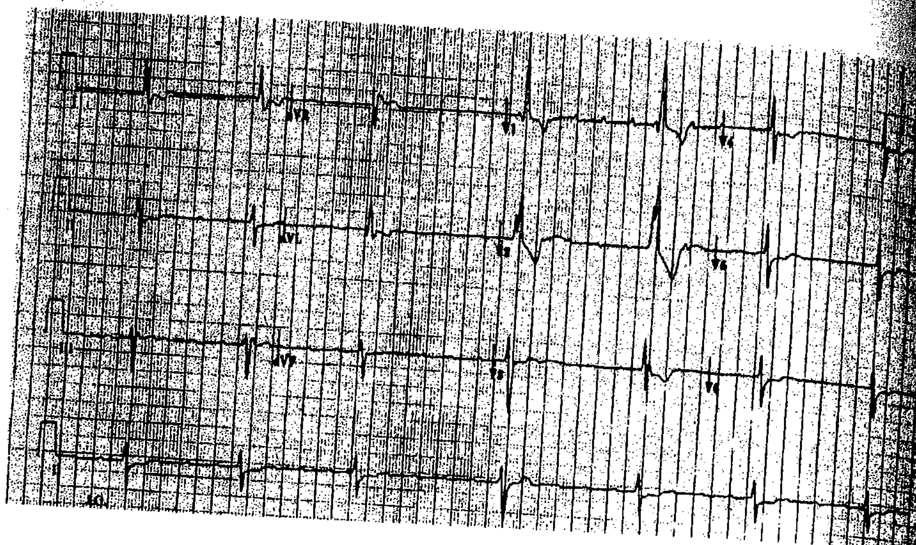


Figure 62–1. Electrocardiograph of a 92-year-old woman demonstrating a high-degree heart block with a ventricular rate of 30–50 beats/min.

administered for the bradycardia but did not increase heart rate; subsequently, 5 vials of digoxin-specific Fab IV were administered over 15 minutes. Within 20 minutes of the infusion, her heart rate had increased to 86 beats/min. The initial serum digoxin concentration was 3.8 ng/mL (therapeutic range: 0.5–2.0 ng/mL).

HISTORY AND EPIDEMIOLOGY

Although there is evidence in the *Ebers Papyrus* (Papyrus Smith) that the Egyptians used plants containing cardioactive steroids at least 3000 years ago, it was not until 1785, when William Withering wrote the first organized account about the effects of the foxglove plant, that the use of cardioactive steroids was more widely accepted into the Western apothecary. The discussion and case reports of the 163 patients for whom Withering prescribed foxglove and his correspondence with other physicians on the subject, comprise the first work related to the medical use of cardioactive steroids. Foxglove was initially used as a diuretic and for the treatment of "dropsy"(edema), and Withering eloquently described its "power over the motion of the heart, to a degree yet unobserved in any other medicine."[122]

Subsequent to these reports, cardioactive steroids became the mainstay of treatment for congestive heart failure, and to control the ventricular response rate in atrial tachydysrhythmias. Because of their narrow therapeutic index and widespread use both acute toxicity and chronic toxicity remain important problems.[82] According to the American Association of Poison Control Centers data, between the years 1999 and 2003 there were approximately 10,800 exposures to cardioactive steroid-containing plants with no attributable deaths, and 13,900 exposures to cardioactive steroid containing pharmaceuticals resulting in 73 deaths (Chap. 130).

Toxicity is typically encountered in the very young or the very old. In children, most acute overdoses are unintentional, resulting from dosing errors, often a decimal point error resulting in 10 times the appropriate dose. Adult patients more often have acute

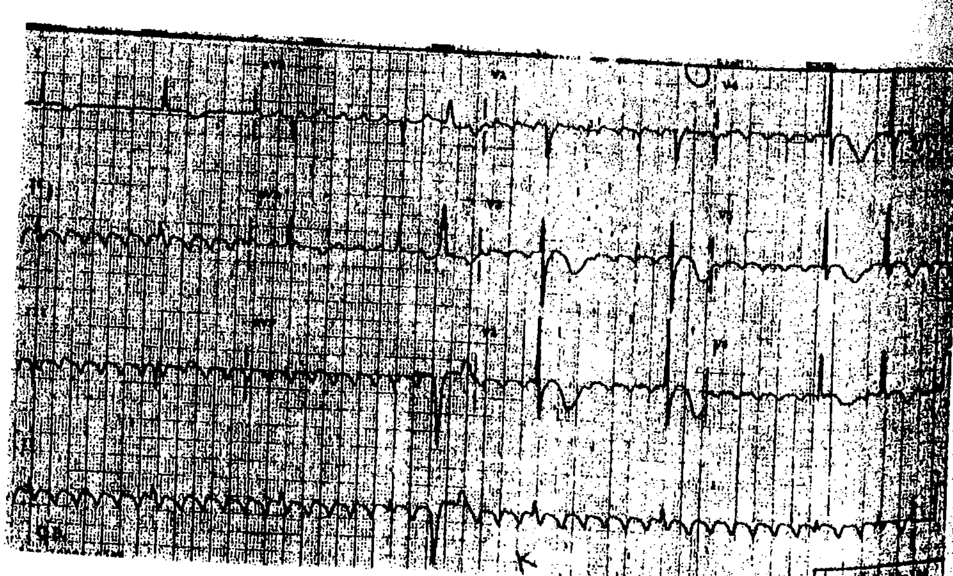


Figure 62–2. Electrocardiograph of the patient in Figure 62–1 after subsequently converted to atrial flutter with variable block and a ventricular rate of 30–40 beats/min.

osures related to intentional ingestions. Older adults are at par-lar risk for toxicity, either from interactions of the cardioactive oids with their chronic regimen of other medications, or indi-ly, as a consequence of an alteration in the absorption or elimi-on kinetics of their therapeutic cardioactive steroid. Drug–drug ractions may change cardioactive steroid clearance in the liver kidney, may alter protein binding, or may result in increased availability.

The most commonly prescribed cardioactive steroid in the ited States is digoxin; other, internationally available but much s commonly used preparations are digitoxin, ouabain, lanato-le C, deslanoside, and gitalin. Cardioactive steroid toxicity may so result from exposure to certain plants or animals. Docu-ented plant sources of cardioactive steroids include oleander erium oleander); yellow oleander (*Thevetia peruviana*), which s been implicated in the suicidal deaths of thousands of patients Southeast Asia;[24] foxglove (*Digitalis* spp); lily of the valley Convallaria majalis); dogbane (*Apocynum cannabinum*); and red uill (*Urginea maritima*). Cardioactive steroid poisoning may re-ult from plant branches (oleander); teas containing seeds of these lants; and water and herbal products contaminated with plant car-lioactive steroids (Chap. 43).[15,18,50,77,88,95,114] Toxicity also results om ingestion, instead of the intended topical application, of a urported aphrodisiac derived from the dried secretion of the *Bufo arinus* toad, which contains a bufadienolide-class cardioactive steroid.[9,11,12] Although there are no reported human exposures, reflies of the *Photinus* species (*P. ignitus, P. marginellus,* and *P. pyralis*) contain a cardioactive steroid designated lucibufagin that is similar in structure to the bufadienolides.[29,63]

CHEMISTRY

Cardioactive steroids all contain an aglycone or "genin" nucleus structure with a steroid core, and an unsaturated lactone ring at-tached at C-17. Cardiac glycosides contain additional sugar groups attached to C-3 (see illustration at beginning of chapter). Cardeno-lides are plant-derived aglycones with a 5-member unsaturated lactone ring. The bufadienolide and lucibufagin groups of car-dioactive steroid molecules are mainly animal derived (with such notable exceptions as scillaren from red squill) and contain a 6-member unsaturated lactone ring. When the aglycone digoxigenin is linked to 1 or more hydrophilic sugar (digitoxoses) residues at C-3, it forms digoxin, a cardiac glycoside. The sugar residues con-fer increased water solubility and enhance the ability of the mole-cule to enter cells. Digitoxin's aglycone differs from digoxin's by the lack of a hydroxyl group on C-12, and ouabain differs from digoxin by both the absence of a hydroxyl group on C-12 and the addition of hydroxyl groups on C-1, -5, -10, and -11. The car-dioactive components in toad venom are genins, and lack sugar moieties.

PHARMACOKINETICS

The correlation between clinical effects and serum concentrations is based on steady-state concentrations, which are dependent on many absorption, distribution, and elimination factors (Table 62–1). Although not proven with other cardioactive steroids, they likely fol-low the distribution pattern of digoxin or digitalis in that obtaining a serum concentration before 6 hours after an ingestion (the time at which the tissue concentration has peaked) gives a misleadingly high serum concentration, resulting from its biphasic distribution. After therapeutic dosing, the intravascular distribution and elimi-nation of digoxin from the plasma are best described using a two-compartment model that is achieved over approximately 36–48 hours in patients with normal renal function. The distribution or α phase represents the rapid rise of drug concentration intravascu-larly, which is dependent on whether the method of administration is intravenous or oral. An exponential decline occurs as the drug is rapidly distributed from the blood to the peripheral tissues with a 30-minute distribution half-life. During the distribution phase, most of the intravascular cardioactive steroid leaves the blood and is found in the tissues, resulting in a large volume of distribution (Vd) (eg, digoxin's Vd is 5.0 L/kg with therapeutic use). The β or elimination phase with a half-life of approximately 36 hours repre-sents the drug's total-body clearance, which for digoxin is achieved primarily by the kidneys (70% in a person with normal renal function).[16,44] After a massive acute digoxin overdose, the half-life may be shortened to as little as 13–15 hours because of el-evated serum concentrations, resulting in greater renal clearance prior to distribution to the tissues.[49,109] Even with therapeutic ad-ministration of cardioactive steroids, adjustments to the dosing regimen must be made for physiologic changes associated with age, hypothyroidism, hepatic disease, and renal diseases if the physiologic changes are associated with a decreased creatinine clearance, alkalosis, chronic hypoxemia, myocardial disease, and cor pulmonale, and for electrolyte abnormalities, including hypo-magnesemia, hypercalcemia, hypernatremia, and, commonly, hy-pokalemia, to avoid toxicity. Hypokalemia resulting from a variety of mechanisms, such as the use of loop diuretics, poor dietary in-take, diarrhea, and the administration of potassium-binding resins, enhances the effects of cardioactive steroids on the myocardium and is associated with dysrhythmias at lower serum cardioactive steroid concentrations. Chronic hypokalemia reduces the number

TABLE 62–1. Pharmacology of Selected Cardioactive Steroids

Pharmacology	Digoxin	Digitoxin
Onset of Action		
Oral	1.5–6 h	3–6 h
IV	5–30 min	30 min–2 h
Maximal effect		
Oral	4–6 h	6–12 h
IV	1.5–3 h	4–8 h
Intestinal absorption	40–90% (mean 75%)	>95%
Plasma protein binding	25%	97%
Volume of distribution	6–7 L/kg (adults) 16 L/kg (infants) 10 L/kg (neonates) 4–5 L/kg (adults with renal failure)	0.6 L/kg (adults)
Elimination half-life	1.6 days	6–7 days
Route of elimination	Renal (60–80%), with limited hepatic metabolism	Hepatic metabolism (80%)
Enterohepatic circulation	7%	26%

9-120

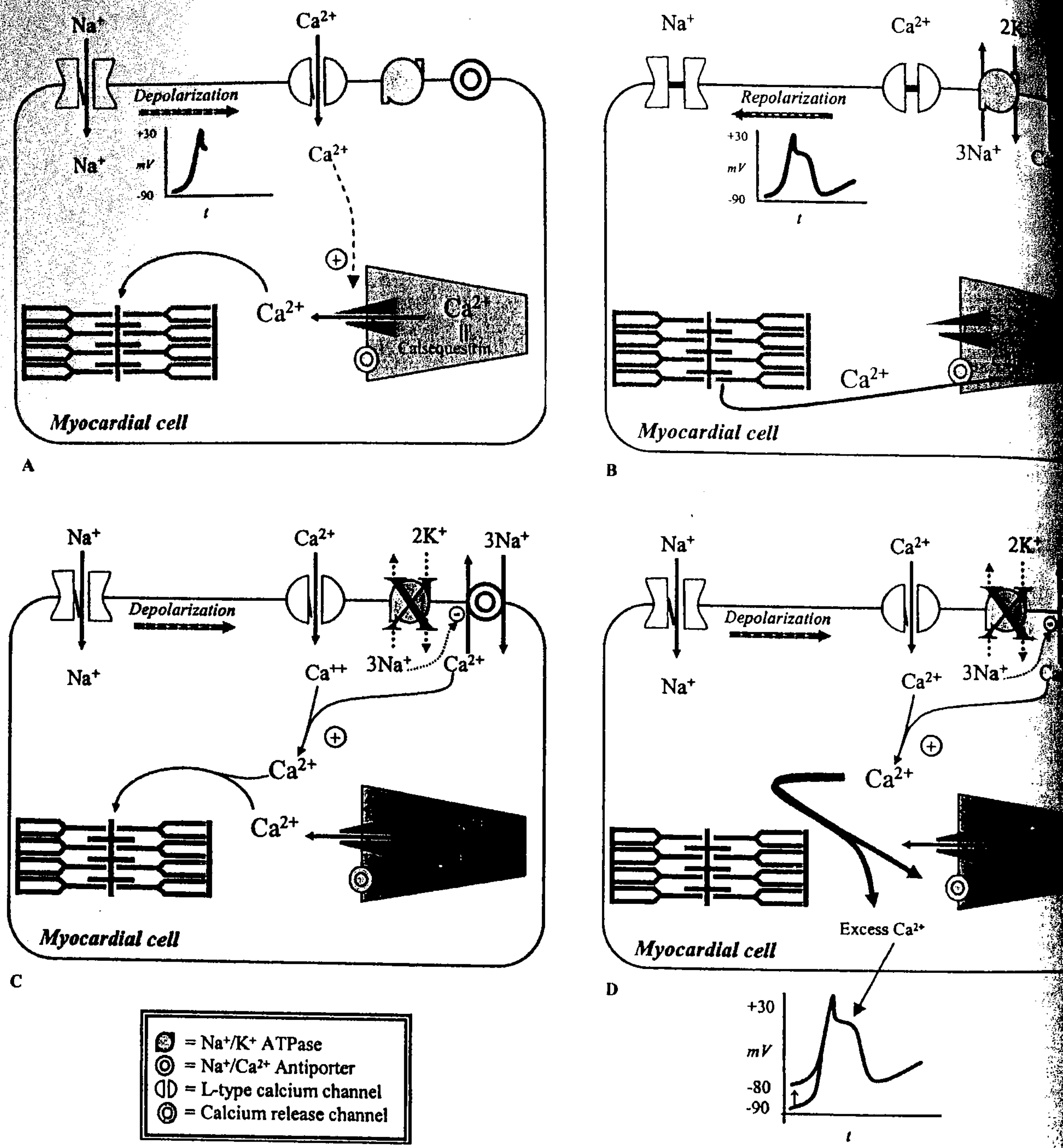


Figure 62–3. **A.** Normal depolarization. Depolarization occurs following the opening of fast Na^+ channels; the rise in intracellular potential opens vo pendent Ca^{2+} channels; and the influx of Ca^{2+} induces the massive release of Ca^{2+} from the sarcoplasmic reticulum, producing contraction. **B.** Norma ization. Repolarization begins with active expulsion of Na^+ ions in exchange for K^+ using an ATPase. This electrogenic (3 Na^+ for 2 K^+) pump creat gradient that is used to expel Ca^{2+} via an antiporter. The sarcoplasmic reticulum resequesters its Ca^{2+} load via a separate ATPase. **C.** Pharmacologic ca steroids. Digitalis inhibition of the Na^+-K^+-ATPase raises the intracellular Na^+ content, preventing the antiporter from expelling Ca^{2+} in exchange for net result is an elevated intracellular Ca^{2+}, resulting in enhanced inotropy. **D.** Toxic cardioactive steroids. Excessive elevation of the intracellular Ca^{2+} el resting potential, producing myocardial sensitization, and predisposes to dysrhythmias. The addition of exogenous Ca^{2+} may overwhelm the capacity o coplasmic reticulum to sequester this ion, resulting in systolic arrest. X = cardioactive steroid.

9-121

...enosine triphosphatase (ATPase) units in skeletal ...by potentially decreasing the volume of drug distri-...

...interactions between digoxin and quinidine, verapamil, ...carvedilol, amiodarone, and spironolactone are com-... These interactions occur because of a reduction of ...binding of the cardioactive steroids, increasing their ...the tissues; a reduction in excretion as a conse-...decrease in renal perfusion; or as a result of interfer-...secretion by the kidneys and intestines because of ...of P-glycoproteins. In approximately 10–15% of ...receiving digoxin, a significant amount of digoxin ...in the gastrointestinal tract by enteric bacterium, *...bacterium lentum.* Inhibition of this inactivation by ...of the gastrointestinal flora by many antibiotics, par-...macrolide antibiotics, may result in increased ... Indeed, the use of certain antibiotics may pro-... as a 2-fold increase in serum cardioactive steroid ...

...ANISMS OF ACTION ...THOPHYSIOLOGY

...logic Effects on Inotropy

...tive steroids increase the force of contraction of the ...inotropic effect) by increasing cytosolic Ca^{2+} dur-... Both Na^+ and Ca^{2+} ions enter and exit cardiac mus-... during each depolarization and contraction. Sodium ... the start of the action potential (phase 0) and car-...ward, depolarizing positive charge. Calcium subse-... the cardiac myocyte through L-type calcium ...during the plateau phase of the action potential, and this ...the release of more Ca^{2+} into the cytosol from the ...reticulum. During repolarization and relaxation (di-... is both pumped back into the sarcoplasmic reticu-...Ca^{2+}-ATPase and is pumped extracellularly by an ...tiporter and a sarcolemmal Ca^{2+}-ATPase (Fig. 62–3;

...tive steroids inhibit active transport of Na^+ and K^+ ...cell membrane during repolarization by binding to a ...on the extracytoplasmic face of the a subunit of the ...Na^+-K^+-ATPase. This inhibits the cellular Na^+ pump ...which decreases Na^+ extrusion and increases Na^+ in the ...thereby decreasing the transmembrane Na^+ gradient. ...the Na^+-Ca^{2+} antiporter derives its power not from ...triphosphate (ATP) but rather from the Na^+ gradient ...by the Na^+-K^+ transport mechanism,[28] the dysfunction ...K^+-ATPase pump reduces Ca^{2+} extrusion from the ...additional cytoplasmic Ca^{2+} enhances the Ca^{2+}-induced ...se from the sarcoplasmic reticulum during systole and ...mechanism increases the force of contraction of the car-...

...on Cardiac Conduction

...peutic serum concentrations, cardioactive steroids also in-...tomaticity and shorten the repolarization intervals of the ...ventricles (Table 62–2). There is a concurrent decrease in ...of depolarization and conduction through the sinoatrial

TABLE 62–2. Electrophysiologic Effects of Cardioactive Steroids on the Myocardium

	Atria and Ventricles	AV Node	ECG
Excitability	↑	—	Extrasystoles, tachydysrhythmias
Automaticity	↑	—	Extrasystoles, tachydysrhythmias
Conduction velocity	↓	↓	↑ PR interval, AV block
Refractoriness	↓	↑	↑ PR interval, AV block, decreased QTc interval

(SA) and (atrioventricular) AV nodes, respectively. This is mediated both indirectly via an enhancement in vagally mediated parasympathetic tone, and directly by depression of this tissue. These changes in nodal conduction are reflected on the ECG by a decrease in ventricular response rate to suprajunctional rhythms and by PR interval prolongation (part of "digitalis effect"). The effects of cardioactive steroids on ventricular repolarization are related to the elevated intracellular resting potential caused by the enhanced availability of Ca^{2+}, and manifest on the ECG as QTc interval shortening and ST segment and T-wave forces opposite in direction to the major QRS forces. The last effect results in the characteristic scooping of the ST segments (the second part of which is referred to as *digitalis effect*) (Fig 62–4). Excessive increases in intracellular Ca^{2+}, caused by excessive cardioactive steroid effects, result in delayed afterdepolarizations. These are fluxes in membrane potential caused by spontaneous Ca^{2+}-induced Ca^{2+} release, which is caused by the excess Ca^{2+}, and appear on the ECG as U waves. Occasionally, these may initiate a cellular depolarization that manifests as a premature ventricular contraction (Chap. 23).[27,58]

Hypokalemia inhibits Na^+-K^+-ATPase activity and contributes to the pump inhibition induced by cardioactive steroids, enhances myocardial automaticity, and, as a consequence, increases myocardial susceptibility to cardioactive steroid-related dysrhythmias. This may be partly a result of decreased competitive inhibition between the cardioactive steroid and potassium at the Na^+-K^+-ATPase exchanger.[93] Severe hypokalemia (<2.5 mEq/L) reduces the rate of sodium pump function, slowing the pump and exacerbating concomitant sodium pump inhibition, because of cardioactive steroids.[58]

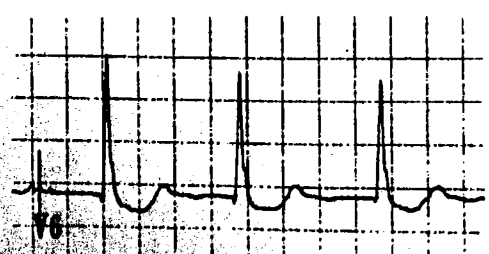


Figure 62–4. Digitalis effect noted in the lateral precordial lead, V6. Note the prolonged PR interval and the repolarization abnormality (scooping of the ST segment).

9-122

Effects of Cardioactive Steroids on the Autonomic Nervous System

Cardioactive steroids affect the parasympathetic system by increasing the release of acetylcholine from vagal fibers,[73,112] possibly through augmentation of intracellular calcium. Cardioactive steroids affect the sympathetic system by increasing efferent sympathetic discharge,[83,107] which, in turn, may exacerbate dysrhythmias.

CLINICAL MANIFESTATIONS

Both adults and children with acute cardioactive steroid poisoning present in a similar manner, as do adults and children with chronic poisoning. However, the clinical manifestations in both adults and children vary based on the chronicity of the exposure.

Noncardiac Manifestations

Acute Toxicity. An asymptomatic period of several minutes to several hours may follow a single, orally administered, toxic dose of cardioactive steroid. The first symptom is typically nausea, vomiting, or abdominal pain. Central nervous system effects of acute toxicity can include lethargy, confusion, and weakness that are not caused by hemodynamic changes.[15]

Chronic Toxicity. Chronic toxicity is often difficult to diagnose as a result of its insidious development and protean manifestations. Symptoms may include those that occur with acute poisonings; however, they are often less obvious. Gastrointestinal symptoms include anorexia, nausea, vomiting, abdominal pain, and weight loss. Neuropsychiatric disorders include delirium, confusion, disorientation, drowsiness, headache, hallucinations, or rarely, seizures.[15,36,37] Visual disturbances include transient amblyopia, photophobia, blurring, scotomata, photopsia, decreased visual activity, and aberrations of color vision (chromatopsia), such as yellow halos (xanthopsia) around lights.[67,68]

Electrolyte Abnormalities. Elevated serum potassium concentrations frequently occur in patients with acute cardioactive steroid poisoning.[58,61] Hyperkalemia has important prognostic implications, as the serum potassium concentration is a better predictor of lethality than either the initial ECG changes or the serum cardioactive steroid concentration.[4,5] In a study of 91 acutely digitoxin-poisoned patients, conducted before digoxin-specific Fab was available, approximately 50% of the patients with serum potassium concentrations of 5.0–5.5 mEq/L died. Although a serum potassium concentration lower than 5.0 mEq/L was associated with no deaths, all of the 10 patients with serum potassium concentration above 5.5 mEq/L died.[4] This hyperkalemia causes further hyperpolarization of myocardial conduction tissue, in particular, increasing AV nodal block, thereby exacerbating cardioactive steroid-induced bradydysrhythmias and conduction delays.[58] However, correction of the hyperkalemia alone does not increase patient survival,[4] as it is a marker of, not the cause of, the morbidity and mortality associated with cardioactive steroid poisoning. Elevation of the serum potassium concentration after administration of cardioactive steroids is a result of cardioactive steroid inhibition of the Na^+-K^+-ATPase pump, which results in the inhibition of potassium uptake in exchange for Na^+ by skeletal muscle (the largest potassium reservoir). The interrelationships between intracellular and extracellular potassium and cardioactive steroid therapy are complex and incompletely understood.

Cardiac Manifestations. The alterations in cardiac rate and rhythm occurring with cardioactive steroid poisoning can produce almost every known type of dysrhythmia with the exception of the rapidly conducted supraventricular tachydysrhythmias. In 10–15% of cases, the appearance of an ectopic ventricular rhythm is the first sign of toxicity, and this is the most frequent rhythm disturbance noted.[92] Although no dysrhythmia is pathognomonic of cardioactive steroid toxicity, toxicity should be suspected when there is evidence of increased automaticity in combination with depressed conduction through the SA and AV nodes.[58] Bidirectional ventricular tachycardia is nearly diagnostic, although it can also occur with poisoning by aconitine and a few other uncommon xenobiotics[103] (Fig. 5–13). These dysrhythmias result from the complex electrophysiologic influences on both the myocardium and conduction system of the heart resulting from direct, vagotonic, and other autonomic actions of the cardioactive steroids. The effects of digoxin vary with the dose, and differ, depending on the type of cardiac tissue involved. The atrial and ventricular myocardial tissues exhibit increased automaticity and excitability, resulting in extrasystoles and tachydysrhythmias. Conduction velocity is reduced in both the atrial conducting system and nodal tissue, resulting in an increased PR interval and AV nodal block. Indeed, AV junctional blocks of varying degrees, associated with increased ventricular automaticity, are the most common manifestations, occurring in 30–40%, of patients with cardioactive steroid toxicity.[74] Atrioventricular dissociation can result from suppression of the dominant pacemaker with escape of a secondary pacemaker, or from inappropriate acceleration of a ventricular pacemaker. Hypotension, shock, and cardiovascular collapse can ensue. Table 62–3 summarizes these phenomena.

Acute Toxicity. The initial increased vagal tone at the SA and AV nodes results in an atropine-responsive bradydysrhythmia. There are a multitude of cardiac dysrhythmias associated with cardioactive steroid toxicity unified by a sensitized myocardium and a depressed AV node (Table 62–3).

TABLE 62–3. Cardiac Dysrhythmias Associated with Cardioactive Steroid Poisoning

Myocardial irritability
Atrial flutter and atrial fibrillation with block
Nonparoxysmal atrial tachydysrhythmias with block
Premature ventricular contractions
Nonsustained ventricular tachycardia
Delayed afterdepolarizations
Bidirectional ventricular tachycardia
Ventricular bigeminy
Ventricular fibrillation
Conduction system dysfunction
AV dissociation
Exit blocks
High-degree AV block
His-Purkinje dysfunction
Junctional tachycardia
SA nodal arrest
Sinus bradycardia

9-123

Chronic Toxicity. Bradydysrhythmias that appear later in acute poisonings, and those that occur in patients with chronic cardioactive steroid toxicity, occur by direct actions of the drug on the heart and often are minimally responsive to, or cannot be corrected by, atropine administration. Ventricular tachydysrhythmias are more common in patients with chronic or late acute poisoning than in patients with early acute poisoning.

Diagnostic Testing

Properly obtained and interpreted serum digoxin concentrations significantly aid in the management of patients with suspected digoxin toxicity, as well as in the management of patients poisoned by several other cardioactive steroids. Although most institutions report a therapeutic range for serum digoxin concentration from 0.5–2.0 ng/mL (SI units: 1–2.6 nmol/mL), current research suggests lowering the upper limit to 1.0 ng/mL to maintain benefit while lowering the risk of toxicity.[96,105] Regardless of the therapeutic serum concentration range used, it must be interpreted in relation to the clinical condition of the patient; the relationship of the time of obtaining the blood sample to that of the last dose; and to other metabolic abnormalities and medications, including hypokalemia, hypomagnesemia, hypercalcemia, hypernatremia, alkalosis, hypothyroidism, hypoxemia, and catecholamines, and the use of calcium channel blockers, quinidine, amiodarone, or diuretics.

Although cardioactive steroid poisoning is multifactorial, resulting from the interactions of the many diverse factors previously mentioned, there is a significant correlation between the clinical condition and the serum concentration. In general, patients with pharmaceutical cardioactive steroid toxicity have mean serum concentrations above 2 ng/mL, measured at least 6 hours postingestion for digoxin, and above 40 ng/mL for digitoxin.[57] The significance of these concentrations depends on when the value is obtained in relation to an acute ingestion and the distribution phase of the drug (as discussed above). A value of 15 ng/mL of digoxin is, therefore, more ominous 6 hours after an ingestion than 1 hour after an ingestion. Because there are multiple determinants of digoxin toxicity, there is an overlap in serum digoxin concentrations between toxic and nontoxic patients, and it may be inaccurate to use the therapeutic range of digoxin of 0.5–2.0 ng/mL as the sole indicator of toxicity.[99]

In most hospitals, "digoxin levels" are the only estimation available to physicians in the acute setting when evaluating a patient for presumed cardioactive steroid poisoning. The polyclonal assays typically used in most institutions frequently, but unpredictably, cross-react with other plant- or animal-derived cardioactive steroids. Although only digoxin is accurately detected by monoclonal digoxin immunoassay, an elevated serum digoxin concentration in the correct clinical setting may qualitatively assist in making a presumptive diagnosis of nondigoxin cardioactive steroid poisoning (Chaps. 43 and 114).[13,86] For example "digoxin" concentrations are recorded from serum spiked with oleandrin and oleandrigenin from *Nerium oleander*, from patients after exposure to *Thevetia peruviana* (yellow oleander) or toad secreted bufadienolides, using various techniques including high-performance liquid chromatography (HPLC) and monoclonal and polyclonal antibody analysis.[9,25,52] With the use of more specific analytic technology, patients with cardioactive steroid poisoning from plant- or animal-derived cardioactive steroids may have low or nonexistent digoxin concentration (Chaps. 43 and 114).

Serum concentrations of digoxin are measured in one of two ways: free digoxin and total digoxin. The most common method of quantifying total digoxin in the serum is by fluorescence polarization immunoassay (FPIA). Under normal circumstances, measuring total digoxin in the serum is sufficient, as serum concentrations are predictive of cardiac concentrations.[23] However, after the use of digoxin-specific Fab (which remains almost entirely within the intravascular space [Vd of 0.40 L/kg]), there is a large elevation in total cardioactive steroid concentrations because the cardioactive steroid is drawn from the tissues and complexes with the antibody fragment, thus trapping the cardioactive steroid in the intravascular space. When this bulk movement is reversed by binding with Fab fragments, a tremendous increase, often approaching an order of magnitude, in total serum digoxin concentrations, occurs. In this situation, methods that detect only unbound digoxin, including treatment with Fab denaturing agents, ultrafiltration, and equilibrium dialysis, allow the quantification of free digoxin in the serum.[34] Paradoxically, excess digoxin antibody can cause a false elevation in the apparent "digoxin concentration" (Chap. 7).

ENDOGENOUS DIGOXINLIKE IMMUNOREACTIVE SUBSTANCE

Some patients who are not receiving a cardioactive steroid may have a positive digoxin assay as a result of an endogenous substance that is structurally and functionally similar to the prescribed cardioactive steroids.[43] This finding is described in patients with increased inotropic need or reduced renal clearance, including neonates;[115] and patients with renal insufficiency,[10,38,51] liver disease,[79] subarachnoid hemorrhage,[121] congestive heart failure,[40,100] insulin-dependent diabetes,[33] stress,[37,116] acromegaly,[24] hypothermia;[115] after strenuous exercise;[116] and in pregnancy.[31,39,48] An endogenous Na^+-K^+-ATPase inhibiting dihydropyrone-substituted bufenolide cardioactive steroid has been isolated from human placenta. It differs from the toad bufadienolides solely by a single double-bond pyrone ring. Because bufenolides are not normally found in either healthy humans or edible plants, a synthetic pathway to produce dihydropyrone-substituted steroids in humans may be responsible for this endogenous digoxinlike immunoreactive substance (EDLIS). Further research is necessary to confirm this pathway.[48] The use of ultrafiltration techniques, while altering incubation time and temperature at which the digoxin assay is performed, can eliminate the contribution of EDLIS.[32] The clinician suspecting this problem should consult the clinical laboratory. Clinical observations indicate that the serum digoxin concentration contributed by endogenous digoxinlike immunoreactive substances is usually less than 2 ng/mL. Other endogenous substances, such as bilirubin,[79] and exogenous substances, such as spironolactone,[101] can cross-react with the digoxin assay and cause a false-positive result.

THERAPY

Management Overview

Initial treatment of a patient with acute cardioactive steroid poisoning includes providing general supportive care, discontinuing cardioactive steroid therapy, preventing further exposure, preventing further gastrointestinal (GI) absorption, monitoring for

digitalis-poisoned patients, 51 patients were treated with cardiac pacing and/or digoxin-specific Fab, and the overall mortality rate was 13%.[111] Prevention of life-threatening dysrhythmias failed in 8% of patients treated with immunotherapy and in 23% of patients treated with internal pacemakers. The main reasons for failure of digoxin-specific Fab was pacing-induced dysrhythmias and delayed or insufficient doses of digoxin-specific Fab. Iatrogenic complications of pacing occurred in 36% of patients. Thus, overdrive suppression with a temporary transvenous pacemaker should not be used to abolish ventricular tachydysrhythmias in the presence of cardioactive steroid poisoning.[5,111] Pacemakers have limited utility and substantial risks in patients with cardioactive steroid toxicity, making the use of digoxin-specific Fab first-line therapy.[111]

Transthoracic electrical cardioversion for atrial tachydysrhythmias, in the setting of digoxin poisoning, is both clinically and experimentally associated with the development of potentially lethal ventricular dysrhythmias. The dysrhythmias are similar to digoxin toxic rhythms,[97] and related to the degree of toxicity, and the amount of administered current in cardioversion.[97] In cardioactive steroid-poisoned patients with unstable rhythms, such as hemodynamically unstable ventricular tachycardia and ventricular fibrillation, cardioversion and defibrillation, respectively, are indicated.

Electrolyte Therapy

Potassium. Hypokalemia and hyperkalemia can exacerbate cardioactive steroid cardiotoxicity. When hypokalemia is noted in conjunction with tachydysrhythmias or bradydysrhythmias, potassium replacement should be administered with serial monitoring of serum potassium, because iatrogenic hyperkalemia is detrimental. In this setting, digoxin-specific Fab administration generally should not be used until the hypokalemia is corrected because the reinstitution of Na^+-K^+-ATPase function may cause profound hypokalemia.

In the presence of acute cardioactive steroid toxicity, when potassium exceeds 5.0 mEq/L, digoxin-specific antibodies are indicated. When marked hyperkalemia develops in conjunction with ECG evidence of hyperkalemia, and if digoxin-specific Fab is not available immediately, an attempt should be made to lower the serum potassium with IV insulin, dextrose, sodium bicarbonate, and oral administration of the ion-exchange resin sodium polystyrene sulfonate. Similar caution, as stated above, should be applied to the subsequent administration of digoxin-specific Fab because of concern for profound hypokalemia. Calcium chloride is beneficial in most hyperkalemic patients, but in the presence of cardioactive steroid, poisoning by calcium salts may be disastrous, as intracellular hypercalcemia is already present. Although a 2004 study was unable to show an adverse effect,[41] a number of experimental studies cite the additive or synergistic actions of calcium and cardioactive steroids on the heart, resulting in dysrhythmias,[35,81,102] cardiac dysfunction[59] (eg, hypercontractility, or the so-called stone heart, hypocontractility), and cardiac arrest.[70,102,117] Furthermore, 3 case reports[7,62] of deaths in cardioactive steroid-poisoned patients following calcium administration support the withholding of calcium administration in the setting of hyperkalemia. The purported mechanism is augmented intracellular cytoplasmic Ca^{2+}, which results from an increased transmembrane concentration gradient that further inhibits calcium extrusion through the Na^+-Ca^{2+} exchange and/or increased intracytoplasmic stores.[57] This additional cytoplasmic calcium may result in altered contraction of myofibril organelles,[59] less negative intracellular resting potential that allows delayed afterdepolarizations to reach firing threshold,[45,57,81] altered function of the sarcoplasmic reticulum,[59,93] or increased calcium interfering with myocardial mitochondrial function (see Chap. 23).[59] Although some investigators suspect that the rate of administration of the calcium may be a factor in the subsequent cardiac toxicity,[70,81] calcium administration should be avoided, as there are better, safer, alternative treatments available for cardioactive steroid-induced hyperkalemia (eg, digoxin-specific Fab, insulin and sodium bicarbonate).[7,35,62,81,102]

Magnesium. Hypomagnesemia may also occur in cardioactive steroid-poisoned patients, secondary to the contributory factors mentioned with hypokalemia, such as long-term diuretic use to treat congestive heart failure. Concomitant hypomagnesemia may result in refractory hypokalemia, despite potassium replacement.[120] The theoretical benefits of magnesium therapy include blockade of the transient inward calcium current, antagonism of calcium at intracellular binding sites, decreased cardioactive steroid-related ventricular irritability, and blockade of potassium egress from cardioactive steroid-poisoned cells.[3,30,53,87,98,108,120] Although hypomagnesemia increases myocardial digoxin uptake and decreases cellular Na^+-K^+-ATPase activity, there is conflicting evidence on whether magnesium "reactivates" the cardioactive steroid-bound Na^+-K^+-ATPase activity.[79,98,108]

The successful use of intravenous magnesium sulfate in the treatment of ventricular tachydysrhythmias, caused by digoxin toxicity, is reported, even in the presence of elevated serum magnesium levels.[60] The mechanism of efficacy of magnesium may be its ability to suppress delayed afterdepolarizations, prolong refractory period by decreasing calcium uptake and potassium efflux,[108] activate Na^+-K^+-ATPase as an essential metallo-coenzyme, or antagonize digoxin at the sarcolemma Na^+-K^+-ATPase pump. However, this treatment is only temporizing, until digoxin-specific Fab is available for definitive therapy, and is not advocated as first-line therapy. The precise dosing of magnesium sulfate in cardioactive steroid-poisoned patients is not established.[3,30,53,60,87,98,120] A common regimen uses 2 g of magnesium sulfate IV over 20 minutes in an adult (25–50 mg/kg/dose to a maximum of 2 g in a child). Following stabilization, an adult patient with severe hypomagnesemia may require a magnesium infusion of 1–2 g/h (25–50 mg/kg/h to a maximum of 2 g in a child), with serial monitoring of serum magnesium levels, telemetry, respiratory rate (observing for bradypnea), deep-tendon reflexes (observing for hyporeflexia), and monitoring of blood pressure. Magnesium is contraindicated in the setting of bradycardia or atrioventricular block, preexisting hypermagnesemia, and renal insufficiency or failure.

Extracorporeal Removal

Forced diuresis,[64] hemoperfusion,[75,118] and hemodialysis[118] are ineffective in enhancing the elimination of digoxin because of its large volume of distribution (4–10 L/kg), which makes it relatively inaccessible to these techniques. Because of its high affinity for tissue proteins, approximately 10 times less digoxin is found in the serum than is found at the tissue level, and of that amount, approximately 20–40% is protein-bound.[55]

Various investigations into new methods of extracorporeal removal are under investigation. Plasmapheresis may have a role for removing retained Fab-digoxin complexes to prevent rebound toxicity after digoxin overdose treatment in anuric patients, but its usefulness has not been clearly defined.[14,85] Additionally, there is a suggestion that hemoperfusion through a β_2-microglobulin adsorptive column might be useful for treating acute digoxin toxicity.[53,113]

9-125

dysrhythmias, determining electrolyte and digoxin concentrations, administering digoxin-specific antibody fragments, and treating specific complications such as dysrhythmias and electrolyte abnormalities.

Gastrointestinal Decontamination

Initial treatment should be directed toward prevention of further GI absorption. Emesis or lavage may be considered only rarely, because efficacy is limited, secondary to rapid absorption from the gut and to the emetic effects of the drug itself. Patients with chronic ingestion do not usually benefit from these GI decontamination techniques, because of the limited availability of drug in the gastrointestinal tract for removal. Because many cardioactive steroids, such as digitoxin and digoxin, are recirculated enterohepatically and enteroenterically, both late and repeated activated charcoal administration (1 g/kg of body weight every 2–4 hours for up to 4 doses) may be beneficial in reducing serum concentrations.[16,65,69,84,119] Steroid-binding resins such as cholestyramine and colestipol,[47,89] like activated charcoal,[20] can prevent reabsorption of cardioactive steroids from the GI tract and reduce the serum half-life by interrupting both enteroenteric and enterohepatic circulation, and may be used in cases where digoxin-specific Fab is not immediately available, or when renal function is inadequate.[20,47]

Advanced Management

Digoxin-Specific Antibody Fragments. The standard of care for patients with life-threatening cardioactive steroid toxicity is the use of digoxin-specific antibody fragments.[1,32,34,85,88,95,104,110,123] Purified digoxin-specific Fab causes a sharp decrease in free serum digoxin concentrations, a concomitant, but clinically unimportant, massive increase in total serum digoxin, an increase in renal clearance of cardioactive steroid, and a decrease in the serum potassium level.[1] In addition, the administration of digoxin-specific Fab is pharmacoeconomically sound.[21] Although the drug itself is expensive, its expense is far outweighed by obviating the need, risk, and expense of long-term ICU stays, and of repetitive evaluation of potassium and digoxin levels. Table 62–4 lists the indications for administering digoxin-specific Fab. Extensive discussion is found in Antidotes in Depth: Digoxin-Specific Antibody Fragments (Fab).

Additional Cardiac Therapies. In the event that digoxin-specific fragments are not immediately available, the secondary drugs for the management of ventricular irritability include phenytoin and lidocaine. These drugs depress the enhanced ventricular automaticity without significantly slowing, and perhaps enhancing, AV nodal conduction.[94] In fact, phenytoin may reverse digitalis-induced prolongation of AV nodal conduction while suppressing digitalis-induced ectopic tachydysrhythmia, without diminishing myocardial contractile forces.[46] In addition, phenytoin can terminate supraventricular dysrhythmias induced by digitalis more effectively than lidocaine.[94] Underlying atrial fibrillation and flutter typically do not convert to a normal sinus rhythm with administration of phenytoin or lidocaine. When used, phenytoin should be infused slowly intravenously (~50 mg/min) or in boluses of 100 mg repeated every 5 minutes until control of the dysrhythmias is achieved or a maximum of 1000 mg has been given in an adult, or 15–20 mg/kg in a child.[8,78] Fosphenytoin has not been evaluated in this setting. Maintenance oral doses of phenytoin 300–400 mg/d in an adult, and 6–10 mg/kg/d in a child, should be continued until digoxin toxicity is resolved. Lidocaine is given as a 1.0–1.5-mg/kg IV bolus followed by continuous infusion at 1–4 mg/min in an adult, or as a 1.0–1.5-mg/kg IV bolus followed by 30–50 μg/kg/min in a child, as required to control the rhythm disturbance. (Chap. 61).

Class IA antidysrhythmics are contraindicated in the setting of cardioactive steroid poisoning because they may induce or worsen AV nodal block and decrease His-Purkinje conduction at slow heart rates, and because of their α-adrenergic receptor blockade and vagal inhibition significant hypotension and tachycardia may occur. Class IA antidysrhythmics are also prodysrhythmogenic and their safety in the setting of cardioactive steroid poisoning is unstudied. Additionally, quinidine reduces renal clearance of digoxin and digitoxin.

In patients with symptomatic supraventricular bradydysrhythmias or high degrees of AV block, atropine 0.5 mg should be administered intravenously to an adult, or 0.02 mg/kg with a minimum of 0.1 mg to a child. Atropine should be titrated to block the vagotonic effects of the cardioactive steroid. The dose may be repeated at 5-minute intervals if necessary. Therapeutic success is unpredictable, because the depressant actions of cardioactive steroids are mediated only in part through the vagus nerve. The use of isoproterenol should be avoided in cardioactive steroid-induced conduction disturbances, as there may be an increased incidence of ventricular ectopic activity in the presence of toxic levels of cardioactive steroids.

TABLE 62–4. Indications for Administration of Digoxin-Specific Antibody Fragments

Any potential digoxin-related life-threatening dysrhythmia
Potassium concentration >5.0 mEq/L in setting of acute digoxin poisoning
Chronic digoxin poisoning with dysrhythmias, significant gastrointestinal symptoms, or acute onset of significantly altered mental status, or renal insufficiency
Serum digoxin concentration (SDC) ≥15 ng/mL at any time, or ≥10 ng/mL 6 h postingestion
Ingestion of 10 mg in adult
Ingestion of 4 mg in a child
To aid in treatment of suspected cardioactive steroid poisoning without a confirmatory level
Poisoning by nondigoxin cardioactive steroid

Digoxin-specific Fab dosing (round up vial calculation)

$$\text{No. of vials} = \frac{\text{SDC (ng/mL)} \times \text{Pt Wt (kg)}}{100}$$

$$\text{No. of vials} = \frac{\text{Amount ingested (mg)}}{0.5\ \text{(mg/vial)}} = 80\%\ \text{bioavailability}$$

Empiric therapy for acute poisoning:
10–20 vials (adult or pediatric)
Empiric therapy for chronic poisoning:
Adult—3–6 vials
Pediatric—1–2 vials

Pacemakers and Cardioversion

External or transvenous pacemakers have limited indications in the management of cardioactive steroid poisoning since digoxin-specific Fab became available. In one retrospective study of 92

9-126

SUMMARY

Digoxin and digitoxin are the most commonly prescribed members of the drugs classified as cardioactive steroids, which share common structural similarities and functions at the cellular level. Cardioactive steroids have a narrow therapeutic index. Signs and symptoms of cardioactive steroid toxicity range from subtle to profound. Both cardiac and noncardiac effects follow cardioactive steroid poisoning. Patients with acute toxicity often have a higher serum concentration of the drug and may present with profound nausea, vomiting, bradycardia, atrial and ventricular ectopy with block, or hyperkalemia. Patients with chronic toxicity often have a lower serum concentration of cardioactive steroids and may present similarly, but more often the symptoms are more protean—loss of appetite, headache, weakness, nausea, alteration in mental status—all of which may be combined with similar ectopic rhythms as with acute toxicity. In addition to overt overdose, an elevation in the serum cardioactive steroid concentrations and an exacerbation of the clinical drug effect leading to toxicity may occur from drug interactions or from deteriorating metabolic processes such as with declining renal function, or from electrolyte abnormalities such as hypokalemia, and hypomagnesemia. A systematic approach toward treating patients using basic supportive and decontamination management techniques, supplemented by the early administration of digoxin-specific Fab immunotherapy can significantly reduce morbidity and mortality in these high-risk patients.

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9-128

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Clinical Investigation and Reports

Impact of Atrial Fibrillation on the Risk of Death

The Framingham Heart Study

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Background—Atrial fibrillation (AF) causes substantial morbidity. It is uncertain whether AF is associated with excess mortality independent of associated cardiac conditions and risk factors.

Methods and Results—We examined the mortality of subjects 55 to 94 years of age who developed AF during 40 years of follow-up of the original Framingham Heart Study cohort. Of the original 5209 subjects, 296 men and 325 women (mean ages, 74 and 76 years, respectively) developed AF and met eligibility criteria. By pooled logistic regression, after adjustment for age, hypertension, smoking, diabetes, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack, AF was associated with an OR for death of 1.5 (95% CI, 1.2 to 1.8) in men and 1.9 (95% CI, 1.5 to 2.2) in women. The risk of mortality conferred by AF did not significantly vary by age. However, there was a significant AF-sex interaction: AF diminished the female advantage in survival. In secondary multivariate analyses, in subjects free of valvular heart disease and preexisting cardiovascular disease, AF remained significantly associated with excess mortality, with about a doubling of mortality in both sexes.

Conclusions—In subjects from the original cohort of the Framingham Heart Study, AF was associated with a 1.5- to 1.9-fold mortality risk after adjustment for the preexisting cardiovascular conditions with which AF was related. The decreased survival seen with AF was present in men and women and across a wide range of ages. **(*Circulation.* 1998;98:946-952.)**

Key Words: fibrillation, atrial ■ mortality ■ prognosis ■ stroke ■ cerebrovascular disorders ■ risk factors ■ aging

Atrial fibrillation (AF) is the most common chronic arrhythmia associated with an adverse prognosis. It is estimated that 2.2 million Americans have intermittent or sustained AF.[1] The incidence of AF increases with advancing age, with an annual incidence per 1000 person-years of about 3.1 cases in men and 1.9 cases in women 55 to 64 years of age, rising to 38.0 and 31.4 cases in men and women 85 to 94 years of age.[2] The clinical risk factors for AF include advancing age, diabetes, hypertension, congestive heart failure, rheumatic and nonrheumatic valve disease, and myocardial infarction.[2] The echocardiographic risk factors for nonrheumatic AF include left atrial enlargement, increased left ventricular wall thickness, and reduced left ventricular fractional shortening.[3] AF is an independent risk factor for stroke, resulting in an approximate 3- to 5-fold excess risk.[4] Furthermore, whereas the attributable risks for most stroke risk factors decline with advancing age, the attributable risks for stroke associated with AF dramatically increase with age, from 1.5% for those 50 to 59 years of age to 23.5% for those 80 to 89 years of age.[4]

See p 943

Although the morbidity of AF is well documented, it has not been clearly established whether AF per se results in excess mortality. The worsened survival seen with AF could reflect the increased mortality of the cardiovascular conditions with which it is associated. Using data from the Framingham Heart Study, we sought to ascertain the mortality associated with AF after adjusting for coexistent cardiac conditions and risk factors in a population-based sample.

Methods

Subjects

The Framingham Heart Study was begun in 1948 to explore risk factors for and consequences of cardiovascular disease in a longitudinal population-based cohort. At entry, 5209 residents of Framingham, Mass, who were 28 to 62 years of age were enrolled. The subjects have received biennial examinations with routine assessment of medical history, physical examination, blood tests, and 12-lead ECGs. The examination procedures were approved by the Investigational Review Board of Boston Medical Center, and all subjects gave informed consent. Previous reports have outlined the

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9-130

TABLE 1. Baseline Characteristics of Subjects With and Matched Subjects Without AF

	Men			Women		
	AF (n=296)	No AF (n=592)	*P*	AF (n=325)	No AF (n=650)	*P*
Mean age, y	73.7	73.8	0.95	76.4	76.4	0.98
Hypertension, %	58.4	54.9	0.33	55.0	53.9	0.76
Smoking, %	27.2	21.1	0.048	21.1	14.1	0.01
Diabetes, %	11.3	14.3	0.22	12.4	7.3	0.01
ECG LVH, %	9.9	6.1	0.052	13.9	6.7	0.0006
Myocardial infarction, %	28.0	14.9	0.0001	14.0	5.6	0.0001
Congestive heart failure, %	21.8	3.2	0.0001	28.9	3.7	0.0001
Valvular heart disease, %	19.4	9.1	0.0001	33.5	12.7	0.0001
Stroke or TIA, %	14.0	9.1	0.04	19.9	8.2	0.0001

LVH indicates left ventricular hypertrophy; TIA, transient ischemic attack. Non-AF subjects were matched to AF subjects by age, sex, and calendar year.

study design, response rates, and completeness of follow-up.[5] For the present study, we analyzed 40 years of follow-up. Subjects were excluded from analysis if they had AF at the first examination (n=19). Analyses were restricted to subjects 55 to 94 years of age at each biennial examination. AF was diagnosed if chronic or paroxysmal AF or atrial flutter was present on ECG. ECGs were obtained from the routine biennial Framingham Heart Study clinic examination or from outside hospitals and physicians.[2]

Definition of Clinical Covariables

Hypertension was considered present if the systolic blood pressure was at least 140 mm Hg or the diastolic blood pressure was ≥90 mm Hg on each of 2 successive readings obtained by the clinic physician or if the subject was receiving antihypertensive medication.[6] Diabetes was defined as a nonfasting blood glucose level ≥11.11 mmol/L (200 mg/dL) or the use of insulin or an oral hypoglycemic agent. ECG left ventricular hypertrophy was diagnosed if a subject had voltage criteria for left ventricular hypertrophy accompanied by lateral repolarization changes.[7] Prevalent congestive heart failure and myocardial infarction were determined by a panel of 3 physicians using previously published criteria.[8] Because echocardiography was unavailable for the first 3 decades of the study, valvular heart disease was defined by auscultation criteria as any diastolic murmur or a >2 over 6 systolic murmur on Framingham Heart Study examination. The diagnosis of a stroke or transient ischemic attack was made by a panel of 3 investigators, including a neurologist, after they reviewed all records from relevant hospitalizations and clinic-reported events. Subjects suspected of having a cerebrovascular event were seen by a study neurologist in the hospital and in periodic follow-up.[9]

Statistical Analyses

The primary analysis examined the impact of AF on mortality in men and women using pooled logistic regression analysis.[10] The pooled logistic regression analysis is equivalent to a Cox time-dependent regression analysis.[10] The pooled logistic regression analyses allowed the covariates in the multivariate models to change over time, with the clinical variables redefined at every biennial examination. Missing data were imputed by substituting the most recent values as long as they were obtained within the 2 preceding examination cycles. Cardiovascular disease was defined as congestive heart failure, myocardial infarction (recognized or unrecognized), and stroke or transient ischemic attack; these events were redefined between biennial examinations as long as they occurred at or before the onset of AF. To assess the net effect of AF, we used multivariate models that adjusted for age, hypertension, smoking, diabetes, ECG left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack unless otherwise specified.

To examine the influence of age and sex on AF mortality, interaction terms were introduced. To remove the impact of conditions with a high case-fatality rate, in 1 analysis, subjects were excluded if they died within 30 days of AF onset. Finally, to investigate whether the poor prognosis with AF was limited to subjects with valvular heart disease or preexisting cardiovascular disease, a multivariate analysis (adjusting for age, hypertension, smoking, diabetes, and left ventricular hypertrophy) was limited to subjects who were free of clinically apparent valvular heart disease, myocardial infarction, congestive heart failure, or stroke or transient ischemic attack.

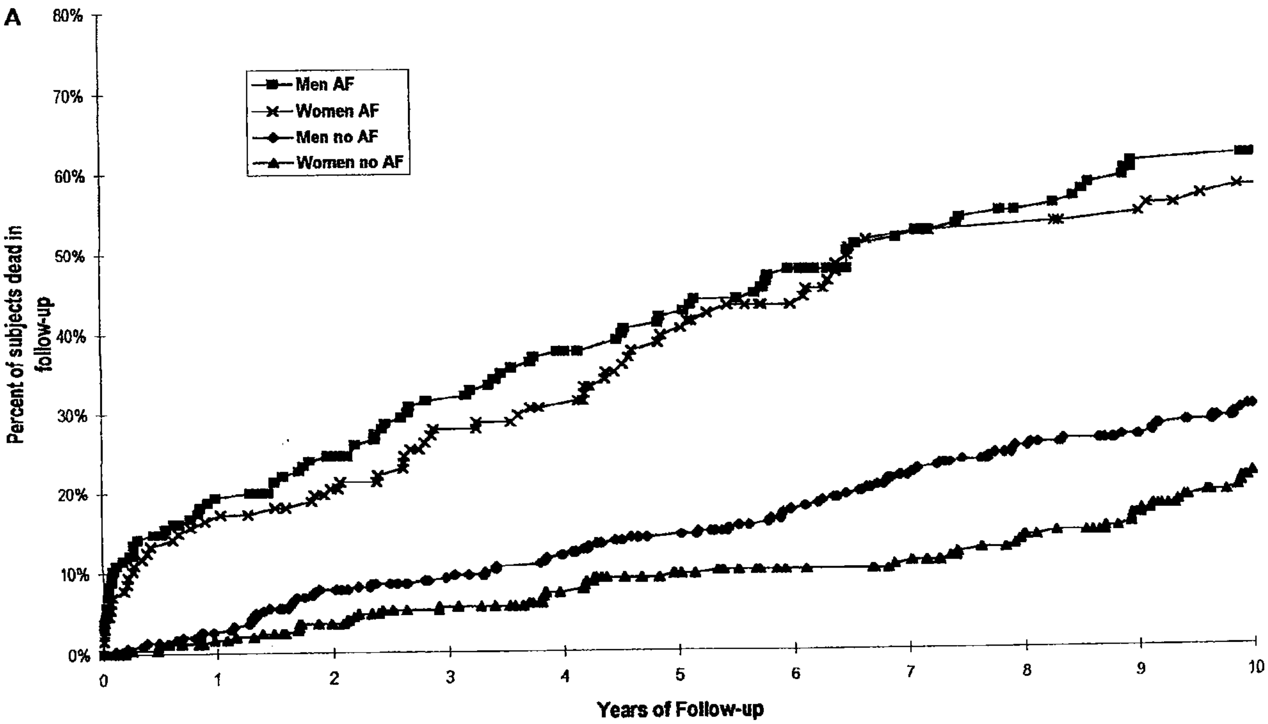
For descriptive purposes, we used a matched-cohort analysis. Approximately 2 subjects without AF were matched to each AF subject by age, sex, and date of diagnosis of AF (index examination cycle). The characteristics of the AF subjects and matched subjects without AF were defined at the baseline index examination. To describe the mortality after AF, a Kaplan-Meier analysis[11] of the matched-cohort subjects was used to estimate survival and produce mortality curves. A log rank test was used to test the differences in survival between AF and matched non-AF participants.[12] All analyses were sex specific and were performed with the Statistical Analysis System program[13] on a Sun Sparc workstation.

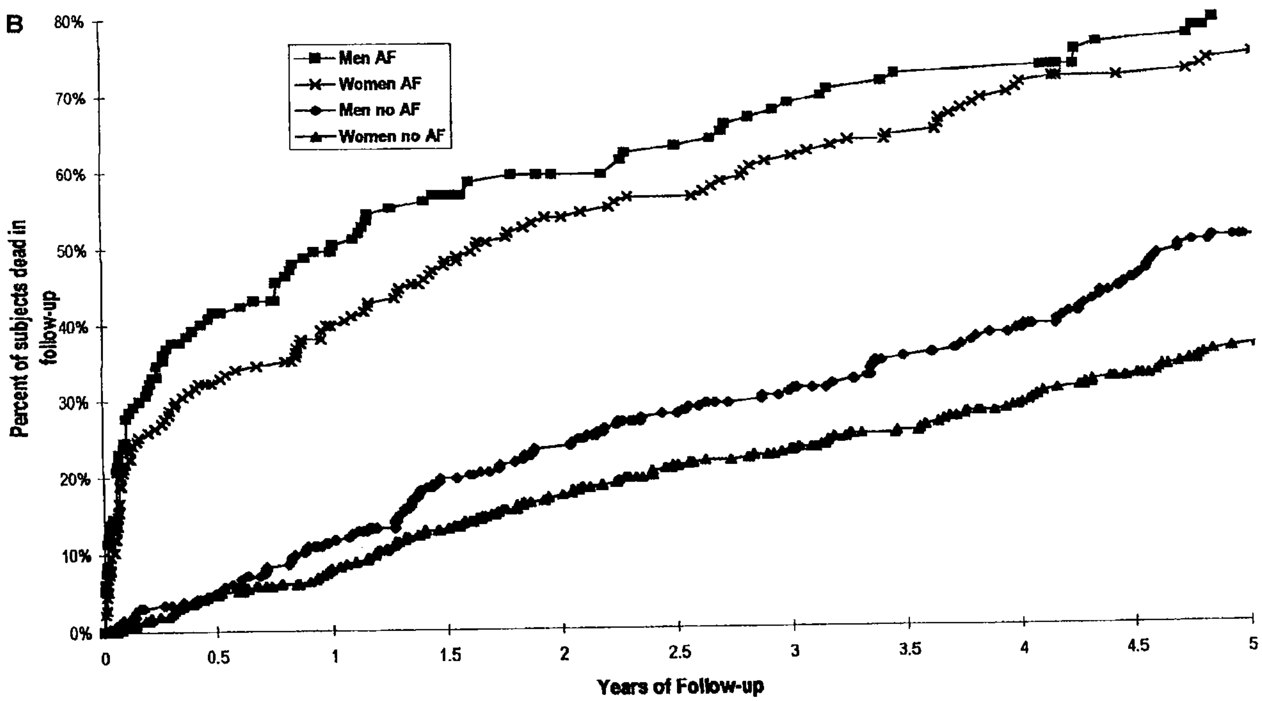
Results

During up to 40 years of follow-up, 296 men (mean age, 73.7 years) and 325 women (mean age, 76.4 years) developed AF. Table 1 displays the baseline characteristics of the AF and the age-, sex-, and calendar year–matched subjects without AF. Subjects with AF were significantly more likely than subjects without AF to have cardiovascular disease risk factors and preexisting disease at baseline, including hypertension, smoking, left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack. In addition, women with AF were more likely to be diabetic.

The Kaplan-Meier mortality curves are displayed in the Figure (top, subjects 55 to 74 years of age at baseline; bottom, subjects 75 to 94 years of age). For both the younger and older age groups, the mortality of men and women with AF was substantially greater than for the non-AF subjects (log rank test, all $P<0.0001$). At 10 years of follow-up, in the subjects 55 to 74 years of age, 61.5% of men with AF had died compared with 30.0% of men without AF; in women, 57.6% of those with AF had died compared with 20.9% of women without AF. Table 2 details the mortality of AF and

9-131





A, Kaplan-Meier mortality curves for subjects 55 to 74 years of age. Vertical axis shows percent of subjects dead at follow-up (0% to 80%); horizontal axis, up to 10 years of follow-up. Subjects included men with AF (n=159), men without AF (n=318), women with AF (n=133), and women without AF (n=266). Both men and women with AF had significantly higher mortality than age-, sex-, and calendar year–matched non-AF subjects. Log rank test for men gave $\chi^2=42.90$ ($P<0.0001$); for women, $\chi^2=70.93$ ($P<0.0001$). B, Kaplan-Meier mortality curves for subjects 75 to 94 years of age. Vertical axis shows percent of subjects dead at follow-up (0% to 80%); horizontal axis, up to 5 years of follow-up. Results are shown for men with AF (n=137), men without AF (n=274), women with AF (n=192), and women without AF (n=384). Both men and women with AF had significantly higher mortality than age-, sex-, and calendar year–matched non-AF subjects. Log rank test for men gave $\chi^2=51.44$ ($P<0.0001$); for women, $\chi^2=101.51$ ($P<0.0001$).

9-132

TABLE 2. Kaplan-Meier Death Rates in Subjects With and Matched Subjects Without AF

Age, y and AF Status	n	30 d, %	1 y, %	5 y, %	10 y, %	Median Survival, y	95% CI
Men							
55–64							
AF	45	8.9	15.6	26.9	43.3	12.6	7.8–16.1
No AF	90	0	2.2	5.6	20.1	18.1	15.6–19.7
65–74							
AF	114	9.9	20.8	48.2	70.3	5.1	3.5–7.1
No AF	228	0	2.7	17.7	34.4	12.3	11.0–13.2
75–84							
AF	106	21.7	44.8	74.8	91.2	1.2	0.8–2.5
No AF	212	0.5	10.2	44.4	73.4	6.2	4.6–7.6
85–94							
AF	31	27.4	65.4	94.7	...*	0.4	0.1–1.1
No AF	62	1.6	13.1	72.6	88.9	2.6	2.0–4.5
Women							
55–64							
AF	35	2.9	11.4	40.0	48.6	12.1	4.4–13.3
No AF	70	0	2.9	7.1	16.1	21.3	17.7–30.2
65–74							
AF	98	8.6	18.2	38.9	62.5	6.4	5.0–9.9
No AF	196	0	1.1	10.5	23.2	16.5	14.1–18.1
75–84							
AF	134	17.2	37.3	66.1	93.9	2.2	1.4–3.3
No AF	268	0.4	6.3	27.9	57.2	8.6	7.2–9.9
85–94							
AF	58	26.4	45.3	96.3	...*	1.3	0.4–1.8
No AF	116	0	11.7	56.3	...*	4.3	3.5–5.4

*Cells with too few observations for stable estimates.

matched non-AF subjects by decade of age and sex. The median survival of men 55 to 64 years of age with AF was 12.6 years compared with 18.1 years in men without AF. Median survival was 12.1 years in women with AF and 21.3 years in women without AF. The excess mortality of the AF subjects was apparent within the first 30 days and persisted throughout follow-up. Furthermore, the excess mortality with AF was observed across all 4 decades of age studied.

To estimate the excess mortality attributable to AF, pooled logistic regression analyses were undertaken (Table 3). For

TABLE 3. Impact of AF on Mortality: Pooled Logistic Regression Analyses

		Men				Women			
Covariates	Subjects at Risk	Deaths/Person-Years	OR	*P*	95% CI	Deaths/Person-Years	OR	*P*	95% CI
Age	All eligible	1465	2.4	0.0001	2.1–2.9	1442	3.5	0.0001	3.0–4.1
		19616				28 439			
Clinical RF	All eligible	1449	1.5	0.0001	1.2–1.8	1438	1.9	0.0001	1.6–2.3
		19 397				28 216			
Clinical RF	30-day survivors	1404	1.1	0.30	0.9–1.4	1391	1.5	0.0001	1.2–1.8
		19 352				28 169			
Clinical RF*	No heart disease or CVD events	599	2.4	0.001	1.8–3.3	660	2.2	0.0001	1.6–3.1
		14 473				22 725			

RF indicates risk factors; CVD, cardiovascular diseases. See text for details. Clinical risk factors include age, hypertension, smoking, diabetes, ECG left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack. Analysis of 30-day survivors eliminated all subjects who died in the first 30 days of follow-up. Analysis of subjects without heart disease or CVD events excludes subjects with valvular heart disease, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack at baseline.

*Clinical risk factors adjusted for were age, hypertension, smoking, diabetes, and ECG left ventricular hypertrophy.

10-133

TABLE 4. Cause-Specific 1 Year Mortality in Subjects by AF Status

	AF Status, Men				AF Status, Women			
	Yes, n (%)		No, n (%)		Yes, n (%)		No, n (%)	
n	296		592		325		650	
Follow-up interval	30 d	30 d–1 y	30 d	30 d–1 y	30 d	30 d–1 y	30 d	30 d–1 y
CHD	10 (3.4)	19 (6.4)	0	10 (1.7)	12 (3.7)	10 (3.1)	0	5 (0.8)
Stroke	6 (2.0)	2 (0.7)	0	2 (0.3)	8 (2.5)	5 (1.5)	0	3 (0.5)
Other CVD	4 (1.4)	5 (1.7)	1 (0.2)	2 (0.3)	7 (2.2)	10 (3.1)	1 (0.2)	4 (0.6)
Other	23 (7.8)	24 (8.1)	1 (0.2)	21 (3.5)	18 (5.5)	17 (5.2)	1 (0.2)	13 (2.0)
Unknown	2 (0.7)	3 (1.0)	0	0	2 (0.6)	6 (1.8)	1 (0.2)	8 (1.2)
Total dead	45 (15.2)	53 (17.9)	2 (0.3)	35 (5.9)	47 (14.5)	48 (14.8)	3 (0.5)	33 (5.1)

CHD indicates coronary heart disease; CVD, cardiovascular disease (not stroke or CHD). Percentages are the percentages of all subjects in the category (eg, male with AF, or male without AF) dying within the specified time interval unadjusted for clinical covariates. Matched cohort analysis (non-AF subjects matched to AF subjects by age, sex, and calendar year).

the pooled logistic regression analyses, 2149 men and 2714 women met eligibility criteria for inclusion at some point during follow-up. Age-adjusted ORs for death with AF were 2.4 in men and 3.5 in women. After multivariate adjustment, with risk factor status at each biennial examination taken into account, AF remained significantly associated with an increased risk of death; the OR with AF was 1.5 in men (95% CI, 1.2 to 1.8) and 1.9 in women (95% CI, 1.5 to 2.2).

Further tests failed to reveal a significant interaction between age and AF with respect to mortality. The multivariate coefficients for an age-AF interaction were 0.00811 (P=0.49) in men and −0.00419 (P=0.69) in women, suggesting that the risk of death with AF did not significantly vary over the 4 decades of age studied. However, the risk of death in the setting of AF did vary by sex. With men and women combined, in a full multivariate model, there was a significant interaction between sex and AF with regard to mortality. The presence of AF made the sexes look similar for mortality: an OR of 1.2 (95% CI, 0.98 to 1.49) for men versus women with AF compared with an OR of 1.6 (95% CI, 1.4 to 1.7) for men versus women without AF.

Secondary analyses explored the impact of AF in subsets of subjects with AF (Table 3). With subjects who died within the first 30 days of follow-up eliminated, AF remained significantly associated with greater mortality in women (OR, 1.5) but not in men (OR, 1.1). Lastly, in an analysis limited to subjects initially free of clinically evident cardiovascular disease and valvular heart disease, AF was associated with a doubling in mortality (multivariate OR, 2.4 [95% CI, 1.8 to 3.3] in men and 2.2 [95% CI, 1.6 to 3.1] in women).

Cause of Death

The mortality rate in the first 30 days and 1 year for the AF subjects and matched subjects without AF are listed in Table 4. The excess mortality observed with AF appeared early; about 15% of subjects with AF died within 30 days of diagnosis. The cause-specific mortality at 1 year suggests that the distribution of the causes of death for the AF subjects was similar to that of the matched subjects without AF (Table 4). However, compared with matched subjects without AF, for each of the causes of death, a higher percentage of the AF subjects died in the first year after AF was diagnosed.

Discussion

These population-based data indicate that subjects with AF have markedly reduced survival compared with subjects without AF, with risk factor–adjusted ORs for death of 1.5 and 1.9 in men and women, respectively. The multivariate analyses suggest that the greater mortality probably was attributable to AF, rather than reflecting the greater burden of risk factors and cardiovascular disease of AF subjects.

We performed secondary analyses to see whether the increased mortality risk was limited to subsets of subjects with AF. One possibility is that AF merely served as a marker for terminal illness. After elimination of 30-day mortality, AF remained associated with a 50% greater mortality in women. However, in men who survived 30 days after AF was diagnosed, AF was no longer significantly associated with increased mortality, suggesting that in men the worsened survival with AF was heavily influenced by early mortality. Another potential explanation is that the increased mortality of AF was confined to subjects with structural heart disease or more severe clinically evident cardiovascular events. When our analysis was limited to subjects free of baseline myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack, AF was still associated with about a doubling in mortality.

Comparison With Previous Literature

Although few would consider AF a benign condition, it has remained unclear whether AF is associated with mortality independent of the coexisting conditions with which it is often observed. The risk of subsets of AF subjects with cardiovascular disease remains controversial. For example, some investigators have reported that after myocardial infarction, AF is associated with excess mortality,[14,15] whereas others have not found an independent effect of AF on post–myocardial infarction mortality.[16,17] Similarly, whether AF is an independent predictor of mortality in subjects with heart failure or stroke is also unclear, with some investigators reporting[18–20] and others refuting[21–23] an independent contribution of AF to mortality.

Evidence of mortality risk in broader series of AF subjects comes from several sources. Gajewski and Singer[24] in 1981 examined insurance applicants and found that after 3.3 years

10-134

of follow-up, applicants with chronic AF or paroxysmal AF in the setting of mitral stenosis or coronary artery disease had increased mortality. In a 1982 hospital-based study, Godtfredsen[25] found that subjects with AF had a worse mortality compared with the general population. A number of cohort studies have also examined the issue, with samples ranging from male air force recruits[26] to male civil servants[27] to population-based samples.[28–32] Given the diverse study designs, it is not surprising that the reported 1-year mortality has varied widely, from 2.6% in the Gajewski and Singer[24] series describing insurance applicants with asymptomatic chronic AF to 16% in patients >70 years of age with AF detected on hospitalization.[33] While 1 study found that the 1.9-fold mortality risk was not statistically significant,[30] most studies have found that AF conferred excess risk of death,[24,26–29,31,32] with a risk of all-cause mortality ranging from an adjusted relative risk of 1.3[26] to an unadjusted relative risk of 2.6.[27]

However, the studies of broader samples of AF subjects have been limited by a number of factors, including a small number of AF cases[29–32] and the inclusion of prevalent AF cases.[24,25,27–30,32,34] Prior studies have also had the disadvantages of being retrospective,[24,25,34] case series,[25,34] or case-control in design.[28,30] Most of the prior studies have not shed light on possible sex differences in the mortality of AF because they have been all male cohorts[26,27] or lacked sex-specific analyses.[24,25,28,30,32,34] With regard to clarifying the independent impact of AF on mortality, the fundamental limitation of most prior studies was their lack of time-dependent or multivariate analyses.[24,25,27,28,30–32,34]

Study Strengths and Limitations

The Framingham Heart Study, by virtue of its longitudinal population-based design, has several advantages. The selection bias inherent in hospital-based series, prevalent AF series, or retrospective series was minimized. In the present series, ECGs were systematically ascertained on all subjects at each biennial examination and by review of outside hospital and physician records. Furthermore, the large number of subjects with AF contained in this series allowed us to analyze the mortality of AF over a broad age range and enabled the separate evaluation of the risk of death in men and women. To the best of our knowledge, the present investigation is the first to examine the relation between sex and AF mortality. We observed a significant interaction between AF mortality and sex, so that AF diminished the typical advantage women enjoy in survival. In addition, the routine collection of clinical history, physical examination, ECGs, and outside hospital records allowed multivariate adjustment for other factors, which may have contributed to the excess mortality seen with AF. A strength of the present study was that pooled logistic regression models were used so that the covariates in the multivariate model were updated at each biennial examination.

The study sample was largely white; our results may not be generalizable to other racial groups. Similarly, the results may not be relevant to subjects outside the age range studied (55 to 94 years of age), particularly younger subjects without any evidence of structural heart disease. In addition, we combined AF and atrial flutter, as well as chronic and paroxysmal AF; hence, we do not comment on differences in the prognosis of these AF subsets. Although the primary analysis controlled for covariates such as myocardial infarction, we were unable to control for infarct severity, which has been associated with risk for both AF and death. Most of the follow-up occurred before the availability of echocardiography and the widespread use of anticoagulants and antiarrhythmics for AF. The lack of routine echocardiography undoubtedly contributed to some misclassification of valvular heart disease. Moreover, we have insufficient data to comment on whether the mortality of AF is altered by anticoagulants[35] or antiarrhythmics,[36] as suggested by others. However, studies suggest that only about one third of eligible AF patients in the United States receive warfarin.[37,38] Therefore, we believe that our mortality data may have relevance to most subjects with AF, given current treatment practices.

Clinical Implications

Several observations suggest that the burden of AF might be expected to rise. The population is aging, and the incidence of AF increases with advancing age.[2] Furthermore, recently published data suggest that the prevalence of AF in the population is increasing even after accounting for age.[39] AF is known to result in substantial morbidity, with a risk factor–adjusted 2.6- to 4.5-fold risk of stroke.[4] The present study demonstrates that AF is independently associated with a 50% to 90% increase in the risk of death. The increased mortality was seen in men and women and was consistent across the 4 decades of age studied. Our investigation supports the contention that AF is associated with excess mortality, which persists after adjustment for coexisting cardiovascular conditions.

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10-135

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10-136

await a transient ischaemic attack[w2] or, even worse, an acute infarction for which an urgent endarterectomy is required[w3] is therefore not good advice. However, others take a contrary view, perhaps because of a lack of facilities, excessive competition rates owing to poor selection of candidates, or inept surgery. Moreover, an attitudinal bias may also exist regarding prevention among doctors who have been trained to intervene only if malfunction of an organ becomes symptomatic.

The degree of stenosis is measured by different methods, and for most specialists 60% stenosis is the cut-off point for selecting patients for endarterectomy. This has led to an erroneous concept that a minimum of 60% stenosis of the internal carotid lumen is the essential criterion.[3] However, other key indicators are turbulent flow caused by stenosis, sludge due to eddy currents, particulate microemboli, and wall abnormalities that are resistant to medical management.[4]

Screening for asymptomatic carotid atherosclerosis by using auscultation for bruits and duplex ultrasonography is feasible and is currently the best way of identifying preclinical atherosclerosis.[5] Patients identified by preliminary screening to determine flow dynamics, arterial wall characteristics including stenosis and ulceration, and microemboli, to identify those for whom medical management is needed and to assess the effect of medical remediation.[6 w4] If medical intervention fails, ACST has proved once and for all that carotid endarterectomy can be worth the risk if surgical and anaesthetic skills are such that operative complications are rare.[7]

International collaborative studies such as these require a huge investment of time, skill, and money and are an endorsement of evidence based medicine first promulgated by Austin Bradford Hill and Sir Richard Doll.[8 w5] For the field of stroke, the baseline from which they evolved were the autopsy findings of Miller Fisher,[w6] followed by the landmark report by Eastcott, Pickering, and Robb at St Mary's Hospital in London.[9] Carotid endarterectomy has now come full circle, having been validated by Halliday, Thomas, and colleagues of the same institution.[2] Their multinational effort continues the search for better methods by which to identify people with atherosclerosis who should be considered for medical and surgical intervention.

So far, differentiating symptomatic from asymptomatic stenosis of the carotid artery has traditionally been the way to decide on treatment. But this requires a doctor skilled in neurology to make the judgment. Moreover, the occurrence of transient ischaemic attacks is not a satisfactory means of categorisation because they are very seldom witnessed, cannot be assessed objectively, are confounded by many other transitory phenomena, and may occur during sleep when they cause no recognisable phenomena or in parts of the brain that do not produce symptoms or signs.[10 11] Moreover, 3-10% of people older than 65 have asymptomatic infarcts visible on brain imaging.[12]

Depending on transient ischaemic attacks for categorising patients is therefore unacceptable as the sole criterion for choosing treatment, and preclinical stenosis and unrecognised transient ischaemic attacks need to be identified by screening.

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Forensic science in the dock

Postmortem measurements of drug concentration in blood have little meaning

Investigations into the circumstances surrounding the death of David Kelly have led to the exchange of acrimonious views including allegations of conspiracy and murder. David Kelly, a government scientist and weapons expert, committed suicide by cutting his wrist and taking painkillers after he was identified in newspapers as the man the UK government believed was the source for a BBC report on Iraq. Impetus for the debate stems mainly from conflicting views about the cause of death, including issues that relate to postmortem toxicology results and their interpretation. Controversy occurs from the mistaken notion that postmortem laboratory measurements, taken in isolation, can be interpreted effectively.

The current controversy illustrates some universally held, but mistaken, notions about the process of death investigation in the United Kingdom and elsewhere. Many assume that forensic pathology is as evidence based as other branches of medicine. This assumption is not accurate.

In the course of caring for living patients, doctors who interpret hospital laboratory tests know, or can quickly find out, the "normal" value for any particular drug. But most doctors (as well as the general public) would be surprised to learn that there are few if any

BMJ 2004;329:636–7

10-137

"normals" in postmortem toxicology. Non-circulating blood after death is not the same thing as circulating blood before death, and evidence that the concepts of normal or therapeutic drug concentrations can be applied to blood from dead bodies is severely lacking.

Even in living bodies, interpretation of a single blood concentration measurement is impossible without considering route of administration, number of doses taken, and the amount of drug actually in the body. Such information is almost never available to investigators, making it impossible to determine the cause of death solely by comparing a single postmortem drug concentration measurement with a range of published values, originally derived from measurements made in living people. With chronic use, tolerance occurs, and tolerance cannot be measured or estimated after death. Healthy patients enrolled in methadone maintenance programmes, for example, may have blood methadone concentrations in excess of other, non-tolerant methadone users examined on the autopsy table.[1] Similarly, we have long known that blood sampled from the heart of a dead person who had been on long term digoxin treatment may contain a seemingly toxic concentration of digoxin when, in fact, the actual blood concentration immediately before death was the appropriate non-toxic therapeutic concentration.[2]

Even if it could be shown that blood concentrations after death were the same as concentrations at the time of death, which blood sample should be used? Drug concentrations are likely to have changed after death.[3] For many drugs, including those found in David Kelly, concentrations may increase by as much as 10-fold.[4] Furthermore, drug concentrations in blood samples from cadavers are site dependent, higher in some locations and lower in others.[5] Should the site yielding the lowest or highest result be used? Or should an average value for three sites be used? Nobody knows because the process has never been studied systematically.

If the blood concentration at the time of death cannot be known with certainty, then how is it possible to extrapolate the time and amount of drug ingested before death? The simple answer is that such extrapolations are prone to considerable error and generally should be viewed as unreliable and not evidence based.[6] Despite these limitations, such calculations are frequently and wrongly produced during court proceedings, even though the problems we outline have been widely known for many years.

Postmortem measurements of drug concentration in blood have scant meaning except in the context of medical history, the sequence and circumstances surrounding death, and necropsy findings. The paucity of evidence based science, coupled with the pretence that such science exists in regard to postmortem toxicology, leads to the abuse of process, almost certainly to the miscarriage of justice, and possibly even to false perceptions of conspiracy and cover up.

We have written this editorial partly because of the Kelly matter, where the central issue concerned the interpretation of the toxicology results. Death investigation and forensic pathology are also not immune to misinterpretation. Poor or inadequate death investigation and incomplete or misinterpreted forensic pathology studies may also result in wrong conclusions. All aspects of the medicolegal death investigation triad—investigation (history), pathology, and laboratory results—are essential and must be evaluated in context with one another. We have formed an ad hoc group to address this issue. A detailed analysis of the problem with suggestions for reform is in preparation.

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Competing interests: appear on bmj.com

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Compulsory registration of clinical trials

Will be a requirement before submission to the BMJ from July 2005

"The case for registering all clinical trials—first advanced a decade ago[1]—is now unanswerable."[2] Editors of the *BMJ* and the *Lancet* made this statement in 1999. Five years of industry resistance, government impotence, and public confusion followed. Medical journals persisted with noble intentions and wise words but were themselves in part resistant, impotent, and confused about how to enforce registration. Some journals, including the *BMJ*, tried an amnesty for unpublished trials, with little success.[3] The *BMJ* also considered asking for compulsory registration, but it seemed to us that trial registries were too diverse, disorganised, and easily disregarded to insist on registration before submission. Nor did we

BMJ 2004;329:637–8

10-138

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